THE PRACTITIONER

No. 1092 JUNE 1959 Volume 182

THE MONTH

The Symposium

WHETHER the solution to the cancer problem will come from the high-powered research institutes or from the casual observation of another Alexander Fleming is still problematical. Be that as it may, in the interim such a mass of reports is being published on the subject that it is impossible for the ordinary clinician to keep in touch with what is going on. Even if he attempts to do so, the technical language in which so many of the reports are couched tends to make 'confusion worse confounded'. It is for this reason that we have devoted the greater part of our symposium this month, on 'Malignant Disease', to a series of articles dealing with the major lines of approach now being pursued by the research workers—epidemiology, biochemistry, viruses, hormones, and heredity. Written by experts in their respective fields, these five articles present a lucid and authoritative review of our present state of knowledge. The symposium concludes with three articles dealing with the more practical aspects of the subject as encountered by the practitioner: cytological diagnosis, carcinoma of the bladder, and carcinoma of the skin.

The Hazards of X-Rays

NO-ONE would deny the undoubted benefits of diagnostic radiology. This is all the more reason why those responsible for ordering and carrying out such examinations should ensure that they are reduced to the lowest possible number and that the exposure for each patient should be the least necessary for effective examination. In its interim report on 'Radiological Hazards of Patients' (H.M. Stationery Office, price 1*s.* 3*d.*) the Adrian Committee gives a reassuring account of the safety of mass miniature radiography. 'Properly conducted examinations of this kind', they say, 'make a negligible contribution to the total radiation to which the population is daily exposed'. The only restriction they propose is that mass miniature radiography should not be used as a case-finding procedure in children or in pregnant women.

Although the report is an interim one, and concerned primarily with mass miniature radiography, the authors lay down some general principles for the reduction of unnecessary x-rays. Two of these are of paramount importance to the clinician. 'There should be clear cut indications before an x-ray examination is requested'. 'Strict control of progress and repeat x-rays is essential'. It is to be hoped that all clinicians will give serious attention to this warning that, by the unnecessary use of diagnostic radiology, the profession is adding to the radiation hazards to which the population is now exposed. Are all the barium meal examinations now being performed really

necessary? How often does the radiological investigation of a duodenal ulcer add anything of value to the management of the case? How often is an x-ray of the spine necessary in a patient complaining of backache? How often does fluoroscopy—in which the dose per examination is much higher than that from radiography—add anything of value to the management of a patient with a failing heart? These are some of the questions which clinicians should be asking themselves. An honestly answered self-questionnaire of this type might well produce a marked fall in the number of radiological examinations carried out every year.

Hospital Diets

'Good food, well cooked and attractively served, is an important part of treatment', according to the 'Third Memorandum on Hospital Diet', published by the King Edward's Hospital Fund for London (price 2*s*.). An excellent precept but, judging from patients' comments, scarcely in accordance with practice in many hospitals. This is certainly not the fault of the 'King's Fund' which, since the end of the last war, has performed yeoman service in the campaign to raise the standards of cooking in hospitals. That much still requires to be done is evident from the elementary facts that it is apparently considered necessary to repeat in a memorandum such as this, of which two may be quoted. 'It is important to ensure that patients are not awakened too early for breakfast, and that the last meal or snack of the day is served late enough'. 'There is still a mistaken idea that the "goodness" of meat is in the gravy'.

Equally disturbing is what the memorandum has to say about kitchen hygiene in hospitals: 'There are still hospitals where so little attention is given to this that hand-basins with hot water are not even provided in or near the kitchens and food stores'. This, of course, emphasizes the statement that 'the outstanding current problem is the structural inadequacy of kitchens in many hospitals which are not only poorly equipped but also badly designed'. Linked with this is the problem of staff shortage and the memorandum puts forward several detailed recommendations for dealing with this. There is a tendency for the 'back-room' physicians and surgeons who are now coming to the fore to overlook the fact that all their expensive drugs, procedures and apparatus are of little avail unless they remember that their 'cases' are also 'patients' who must be fed. Unless hospital diets maintain the highest standards—æsthetically as well as nutritionally—the full benefit cannot be expected from all the advances of this meteoric era of progress in medicine.

Smoking Deterrents

There is no known 'cure' for smoking except will-power. This is no reason, however, why those lacking such power should not be given some assistance. Whether this assistance should come from the hypnotist, the group therapist or the pharmacist is probably of little significance—provided the 'patient' realizes that he himself is the deciding factor in determining whether or not a 'cure' will be achieved. With regard to drug remedies one further proviso must be

added: that the remedy is safe. It is from this point of view that the survey of 'Smoking Cures' in the current issue of *Which?* (No. 7), the journal of the Consumers' Association, is of particular interest.

Details are given of nine 'smoking cures' now currently available: three in the form of cigarettes, three in tablet form, two as capsules, and one as a powder. To these might be added the use of lobeline, a report on which is abstracted in 'Practical Notes' (p. 777). All three 'cigarettes' are made of hollow plastic or wood and filled chiefly with menthol crystals. As *Which?* points out, the inhaling and exhaling of menthol vapour may affect the sense of smell and so make tobacco smoking unpleasant, whilst 'the selective stimulation by menthol of the nerve-endings which respond to cold gives a sense of coolness which some people like'. Of the three tablets, two contain ferrous sulphate and alum whilst the third contains menthol and a bitter extract. Here again, presumably their value is in spoiling the taste of a cigarette. The two capsules would appear to be based on the same principle —each containing quinidine (0.25 g.), camphor and eucalyptus. The powder comes into an entirely different category, as it contains potassium bromide and a small amount of potassium sulphate. Apart from these powders, which should obviously be taken only under medical supervision, none of these preparations would appear to be potentially dangerous. Whether they are beneficial is another matter.

Why Eat Fruit?

FRUIT has always tended to be looked upon as rather a luxury in this country. Whenever money gets tight the first thing the average British housewife saves on is fruit. It is an attractive addition to the meal, liked because of its taste and colour, but seldom regarded as a useful source of nutriment—with the exception of oranges as a source of vitamin C for children, and even here the tendency is to buy the vitamin as tablets from the pharmacist in the form of ascorbic acid. In a lecture delivered before the international congress of pomology in Brussels last autumn, and published in the *Revue Médicale de Liége* (1959, **14**, 252), Professor L. Brull demonstrates two fallacies in this concept.

The three main nutritional contents of fruit are sugar, salts and vitamins. So far as sugar is concerned, apples, pears, prunes and cherries contain 10 to 15 per cent., raisins more than 20 per cent., oranges 12 per cent., and bananas about the same proportion as potatoes. The fruits with the highest content of vitamin A are peaches, apricots and prunes, whilst many fruits contain either vitamin B or vitamin C, the latter being in greatest abundance in citrous fruit. What is often forgotten is that fruit is a rich source of salts, especially calcium, iron and iodides. As a practical demonstration of the nutritional value of fruit, Professor Brull draws attention to the fact that, unlike most other occupied countries during the 1939-45 War, there was very little osteoporosis or anæmia in Belgium. This he attributes to the relative abundance of fruit and vegetables the country was able to grow, thereby

maintaining an adequate supply of essential minerals such as calcium and iron. Meat and fat were in short supply, with resulting loss of weight and nutritional œdema, but home-grown supplies of vegetables and fruit saved the population from many of the ills to which the inhabitants of other enemy-occupied countries were subject. The lesson learned in the hard way by the Belgians might well be taken to heart by those in this country who look upon fruit as a luxury and not as an important part of the household diet.

African Medicine

THE 'new look' in pharmacology and therapeutics should not blind us to the fact that less than thirty years ago the *British Pharmacopœia* contained such delectable items as petals of red roses, grindelia, embelia, alstonia, and leeches. We are therefore not perhaps as far removed from African native medicine as the younger generation of practitioners might like to think. Such thoughts are inevitably uppermost in one's mind on reading an interesting account of 'Sukuma Leachcraft' by Dr. R. E. S. Tanner (*E. Afr. med. J.*, 1959, **36**, 119). The Sukuma, a tribe of over a million people in north-western Tanganyika, have 'an enormous pharmacopœia, probably extending to some thousands of plants'. Dr. Tanner himself collected over 400 specifically medicinal plants.

Their choice of medicaments, however, is not restricted to herbs or plants. Civet dung and pounded tree bark are smoked in a pipe as a cure for tuberculosis, and the cast skin of a mamba for leprosy. Spider's web and various herbs are used as a palliative for persistent vomiting, and 'a mixture of the patient's own blood and tree sap is rubbed into small cuts made on the stomach which is causing sharp pain'. Dew is highly thought of as a cure for cataract, and powdered stone dust from their grinding stones as a cure for sore throat. Distilled spirit, which is proscribed by law, is used for children when they are being weaned, and also as a base for herbal preparations taken for the relief of a persistent cough. A curious finding in their 'pharmacopœia' is a well-known, much advertised effervescent drink which, according to Dr. Tanner, 'sells in quantities because it is regarded as a cure for syphilis'.

An Apology

OWING to circumstances over which we have no control the printing of *The Practitioner*, like that of practically every other publication in the country, may now be subject to unpredictable delays. At the time of going to press there is no definite indication as to the effect of the current dispute in the printing industry upon publication schedules, but we have been warned that there may be a delay in the publication of this issue. Should this occur, we offer our apologies to our readers and trust that they will bear with us in any inconvenience to which they may be put.

THE EPIDEMIOLOGY OF CANCER

By PERCY STOCKS, C.M.G., M.D., F.R.C.P.
Formerly Senior Research Fellow, British Empire Cancer Campaign

EPIDEMIOLOGY is the science which deals with mass phenomena of disease of any kind in man. The use of alternative terms such as 'geographical pathology' for such studies when the disease is not known to be infective is confusing and should be discouraged. Quantitative data about the occurrence of the disease are examined by statistical methods and logic and, if the methods are rigorous and the results consistently support a hypothesis of causation of the disease, such evidence has a validity which does not depend upon confirmation by laboratory experiments. The history of medicine abounds in examples of diseases which were attacked with great success by acting upon epidemiological evidence before the causative agent had been discovered in the laboratory, and a useful survey of such contributions to preventive medicine in the past has been made recently by Ingraham (1958). For example, smallpox vaccination and the cleansing of water supplies and milk resulted from studies of epidemics by Jenner, Snow and Michael Taylor long before anything was known about viruses and bacteria, and they resulted in a vast saving of life. In the long battle against insect-borne diseases statistical studies played an indispensable part, and this has been true also of the initiation of mass immunization processes against diphtheria, yellow fever, tuberculosis and poliomyelitis. Statistics resolved the serum hepatitis riddle and threw unexpected light on the causation of some congenital malformations. Epidemiologists are now working on coronary thrombosis, peptic ulcer, bronchitis and cancer, and already hopes, to which laboratory research has contributed little, are emerging that the incidence of these major causes of invalidity and mortality can be reduced if we really desire it by precautionary actions based on hypotheses.

What useful facts have been found out about cancer by such methods? First of all, occupational cancers of the skin were related statistically to jobs involving continual contact with soot, tar and certain crude oils, with resulting successful preventive measures, and this history is now being repeated for bladder cancer in men who handle certain chemicals. Investigations of the social histories of hospital patients with cancer of various organs or of persons dying of such cancers in comparison with control groups, follow-up studies of large numbers of people of known habits to discover their eventual death rates from cancer, and statistical studies of correlations between mortality in local populations and the environments in which they live, have all produced indications about etiology, some of which have been startling. An account of the results of such studies of breast cancer was given in this journal recently (Stocks, 1957), and it is practicable here only to mention some of the salient facts which have been revealed about cancers of other organs.

CANCER OF THE LARYNX AND ŒSOPHAGUS

Laryngeal cancer is remarkable in showing pronounced epidemiological differences between the sexes. Among males rates are greater in urban than in rural areas and increase according to social class from professional to unskilled; and when analysed by occupation the rates are high among makers and servers of alcoholic drinks. Mortality of females is greater in rural areas, and no class gradient is evident. The distribution of mortality from laryngeal cancer among the large towns of England and Wales is also entirely different in the two sexes, but the rates for each sex are strongly correlated with those of *œsophageal* cancer. The risks of both laryngeal and œsophageal cancers in men are increased in those who have been addicted to alcohol or heavy cigarette smoking.

CANCER OF THE STOMACH

The incidence of cancer of the stomach shows some pronounced geographical variations, being very high in Japan and parts of Wales, and greater in England and Switzerland than in the United States of America, where death rates have been falling substantially. In some countries, but not in all, there is a moderate urban excess, with a high degree of association with poor social conditions. Although death rates are high in such occupations as dock labourers, furnacemen and metal workers in England and Wales, the wives of these men show little or no excess. In the large towns and two northern counties there is a significant connexion with atmospheric pollution after allowing for the density of population in the area. No relation is apparent with alcohol addiction or smoking or with the consumption of beer, milk, tea or green vegetables, but in the Liverpool region some association with the frequency of eating fried foods was found. Welsh people who have been living out of Wales are subject to no greater incidence than English people in the same districts, and the high rates in parts of Wales show no connexion with dietary habits. Mortality tends to be low in geographical areas with underlying chalk or limestone and high where igneous rocks are close to the surface. In North Wales and Cheshire incidence is greater in districts where the soil has a high content of organic matter, and in North Wales it is associated statistically with long residence in houses where the garden soil has an organic carbon content characteristic of seasonal fluctuation of water level in the subsoil. Incidence of this form of cancer shows a specific association with the amount of zinc in the garden soil, and in common with other forms of cancer it appears to be connected also with the amount of chromium.

CARCINOMA OF THE COLON AND RECTUM

Intestinal cancer appears to be less variable geographically than gastric cancer, but incidence is extremely low in Japan for both the colon and the rectum. Death rates tend to be rather higher in urban than in rural areas, and in England and Wales they are high among men engaged in making and serving alcoholic drinks. In the Liverpool and North Wales region an

association with the frequency of beer drinking was found in men, but no correlation with the consumption of wine is evident in France. No connexion is found with the frequency of taking milk, tea, green vegetables or fried foods, or with heavy cigarette smoking, but there appears to be some association between the incidence of rectal cancer and pipe smoking.

CARCINOMA OF THE UTERUS

Cancer of the cervix uteri occurs rarely in virgins and less frequently among single and infertile married women than among those who have had a number of children. Although the rate rises according to the number of children the important factor responsible for this statistical relation appears to be the commencement of frequent intercourse at an early age, but among women who marry late many confinements seem to increase the risk. Jewish and other women in communities where male circumcision and ritual marital hygiene are practised tend to have lower rates of incidence. In the United States rates are higher among white than among coloured women. Death rates in England and Wales are higher in wives of unskilled workers than in wives of professional and skilled workers and the social gradient cannot be accounted for by differential fertility of the classes. Rates tend to be higher in seaports and textile towns.

CARCINOMA OF THE LUNG

Cancer of the lung and bronchus has been certified as a cause of death to a rapidly increasing extent during the last twenty years in most countries where death registration and diagnostic facilities are well developed, and it is now generally agreed that the increase can be only partly accounted for by improving recognition of the disease. The simultaneous and complementary fall in death rates from phthisis suggests some connexion but no conclusive epidemiological evidence has been found for this. Death rates are very high in Britain and Finland, rather high in Holland and Switzerland, low in Norway, Sweden and Iceland and very low in Japan. Whereas twenty-five years ago in England and Wales the registered mortality was greatest in the upper social classes this has now been reversed to a social gradient of the usual kind both here and in Denmark. Occupational differences are not very pronounced but rates above the average have been found for workers with coal gas, tar, asbestos, oil, varnish and certain hot metals and metallic dusts, and in Holland among servers of alcoholic drinks, tobacconists and diamond cutters. In the Liverpool region and North Wales there is a strong positive association between the incidence of lung cancer in men and frequency of beer drinking which is seen alike among non-smokers, cigarette and pipe smokers and is not therefore to be explained by the tendency for excessive drinking and smoking to go together. In France no association has been found with consumption of wine, but frequency of coffee drinking appears to be correlated with lung cancer incidence independently of smoking habits.

CAUSATION OF BRONCHOGENIC CANCER

More than twenty investigations in eight countries, comparing past smoking habits of men with lung cancer with those of control groups, have shown a larger proportion of heavy smokers among the former; three large-scale studies indicate strong correlations between incidence of the disease and the number of cigarettes habitually smoked in each sex. Two 'prospective' studies of the subsequent causes of death of large numbers of men of known smoking histories agree in showing increase of lung cancer death rates according to the number of cigarettes smoked and a lessening of rates

Classification by past smoking histories	Follow-up studies of healthy men of known smoking histories		Retrospective studies comparing lung cancer patients with controls classified by smoking history		
	(a) Doll and Hill	(b) Hammond and Horn	(c) Doll and Hill	(d) Stocks N. Wales	(e) Stocks Liverpool
Ages:	Over 35*	50–69*	45–74	35–74*	35–74*
Non-smokers†	7	13	6 (approx.)	22	50
Pipe only	38	39	120 (approx.)	46	82
Cigarettes per week:					
< 100	95	100	165 (approx.)	68	168
100–	167	120	216	147	248
150–				232	389
175–		229			
200–	276		350		
275–		264		344	387
350–			737		

* Standardized rates. † Never smoked an appreciable amount per week.
(a) Doctors in England and Wales—see Doll and Hill (1956).
(b) Apparently healthy men in U.S.A.—see Hammond and Horn (1958).
(c) Hospital patients mainly in London—see Doll and Hill (1952).
(d) Residents in North Wales seaboard area—see Stocks (1958b).
(e) Residents in Liverpool area—see Stocks (1958b).

TABLE I.—Death rates of men per 100,000 at ages stated, according to smoking habits and numbers of cigarettes as estimated from epidemiological studies.

among those who had ceased smoking. Histological data have led to the conclusion that adenocarcinoma of the lung has not increased in incidence and that it is not connected with smoking. Death rates in England and Wales increase markedly according to the degree of urbanization, size of town and density of population per acre, and in other countries where lung cancer rates are lower and coal is little used for domestic heating a similar but less pronounced urban excess is found. This relation with urbanization appears among non-smokers, light and moderate cigarette smokers and pipe smokers, but seems to be slight or non-existent among heavy cigarette smokers. The rates summarized in table I show the consistent gradient from non-smokers to heavy cigarette smokers in each column; comparisons along horizontal lines cannot be made owing to the different groups of ages used,

except between (d) and (e) which compare men living in a mostly rural area with men in a large city.

In the American study (b) the over-all rates at ages 50 to 69 based on well-established lung cancer, excluding adenocarcinoma and standardized for age and smoking habits, were 39 per 100,000 in rural areas, 46 in towns with 10,000 to 50,000 population and 52 in larger towns; among those who had not smoked they were 0, 9, and 15 respectively. In the most rural parts of North Wales the non-smokers' rate at ages 35 to 74 was 14 (including adenocarcinoma) compared with 50 in the Liverpool area, and the male/female ratio for incidence rates in non-smokers was close to unity in the rural area compared with about 8 to 1 in Liverpool.

Death rates from lung cancer in the large towns of England and Wales are highly correlated with the amounts of atmospheric deposit and smoke and this correlation remains after allowing for differences in population density which may affect the rates in other ways (Stocks, 1959). This is true also for all districts of Lancashire and the West Riding of Yorkshire for which air pollution data are available, and a statistical association is found between death rates and the population density of adjacent areas independently of the density in the district itself, phenomena which are found also for bronchitis and seem to point unmistakably to drifting smoke as the urban factor. In Liverpool and North Wales region the concentrations of benzpyrene and other carcinogenic hydrocarbons in the air agree tolerably well with lung cancer death rates in districts surrounding the points of measurement (Stocks and Campbell, 1955; Stocks, 1958c). The evidence so far gathered by epidemiological studies therefore gives consistent indications of two major causative agents: namely, the smoking of cigarettes and atmospheric smoke.

VALIDITY OF STATISTICAL EVIDENCE

When conclusions based upon epidemiological research are unpleasant and disturbing an easy way of escape is to say that statistics cannot 'prove' anything, and many people are finding this a convenient excuse when faced with such evidence as I have just outlined. In his book on 'Biological Aspects of Cancer' Sir Julian Huxley (1958, pp. 118-119) sums up the matter thus:—

> 'The conclusion to be drawn from the evidence is definite; increased smoking increases the probability of developing lung cancer. Unfortunately the significance of such a statement is not clear to many people. Obsessed by the naïve idea of finding a single cause for every effect, they shake their heads and say that the evidence is only statistical, as if that invalidated it'.

He goes on to explain that every scientific law is in fact statistical rather than absolute, and on this point I venture to quote something I wrote in 1957 (Stocks, 1958a):

> 'Even in physics the behaviour of individual particles cannot usually be predicted, but only the average behaviour of large numbers; and when comparatively small numbers are under observation the problem becomes one of probabilities and

statistical methods become necessary to connect causes with effects. It does not follow, however, that causation ceases to be "provable" when statistical methods have to be invoked. In either case proof can only be based on the consistency of a large number of observations, and in the biological sciences at least causation has to be assumed and acted upon when the consistency is considered to be good enough, for it is never perfect'.

Another excuse for throwing doubt on the epidemiological evidence was commented upon thus by Huxley in his book (pp. 63-64):

'Some workers are still trying to dodge the issue by pointing out that not all those given to heavy cigarette smoking develop lung cancer. It is surely time that we should drop mediæval concepts concerning causation and think in terms of multiple correlation. We then find just what we should expect on the supposition that some substances in tobacco smoke and in exhaust fumes or ordinary smoke are carcinogenic, and that the population varies widely in cancer proneness (susceptibility) to them'.

More reasonable criticism has come from a few expert statisticians on the grounds of some unavoidable bias in the populations studied, but this has been well answered by Hammond (1958) and these faults cannot account for more than a small part of the correlations with smoking in the case of lung cancer although they are important in connexion with some other diseases which appeared to show weak correlations.

Finally, there are those who say that, however strong the statistical evidence may be, we must wait for experimental proof which they regard as sacrosanct, although in fact it usually suffers from the same sort of disabilities as epidemiological evidence. When asked whether he thought that the causes of lung cancer would be established experimentally in the near future, the late Sir Ernest Kennaway surprised many of his hearers by replying that he thought that for a long time we will have to rely upon statistical evidence. In my opinion the inescapable answer to all this is that in face of the rapidly rising mortality from lung cancer and the strength of the evidence jointly incriminating cigarette and atmospheric smoke, everything possible should be done to remove or prevent the production of carcinogens already known to be present, to educate people as to the risks and discourage boys and girls from acquiring the cigarette habit, and to reduce pollution of the air in towns by potentially carcinogenic substances.

References

Doll, R., and Hill, A. B. (1952): *Brit. med. J.*, **ii,** 1271.
——, —— (1956): *Ibid.*, **ii,** 1071.
Hammond, E. C. (1958): *Amer. J. publ. Hlth*, **48,** 1460.
——, and Horn, D. (1958): *J. Amer. med. Ass.*, **166,** 1159.
Huxley, J. (1958): 'Biological Aspects of Cancer', London.
Ingraham, H. S. (1958): *Amer. J. publ. Hlth*, **48,** 1449.
Stocks, P. (1957): *The Practitioner*, **179,** 233.
—— (1958a): 'Cancer', vol. 3, chap. 4, London.
—— (1958b): 'Supplement to 35th Annual Report of the British Empire Cancer Campaign', London.
—— (1958c): *Int. J. Air Pollution*, **1,** 1.
—— (1959): *Brit. med. J.*, **i,** 74.
——, and Campbell, J. H. (1955): *Ibid.*, **ii,** 923.

THE BIOCHEMISTRY OF CANCER

By E. BOYLAND, D.Sc.

Professor of Biochemistry, Institute of Cancer Research, Royal Cancer Hospital

Biochemical investigations into the problem of cancer are now carried out intensively and much new knowledge has been gained in the study of the nature of cancer cells and tissues, of carcinogenesis, and of chemotherapy of cancer and leukæmia. One field in which biochemical research has been less successful is in the elaboration of diagnostic tests for malignant disease. There is still no reliable biochemical diagnostic test for cancer, although there are some reactions, such as the serum acid phosphatase in cancer of the prostate, and the polarographic test in most forms of cancer, which are of prognostic value in following the course of the disease.

The control of cancer could be attained by the discovery of effective chemotherapeutic agents, and the finding of new drugs with specific anti-cancer activity might be facilitated by knowledge of the nature of the chemistry and biochemistry of cancer cells. If a difference between the normal and malignant tissues were found, this should give a lead to new types of chemotherapeutic compounds. In the past, however, this approach, which might be considered rational, has not led to success in the clinical treatment of cancer. Another approach to the problem is by the study of carcinogenesis which may lead to reduction in the incidence of the disease. In the first place this would be achieved by recognition of carcinogens in the environment. Thus, following the discovery that 2-naphthylamine causes cancer of the bladder in man, the manufacture of this compound was stopped in this and some other countries, and the carcinogenic hazard reduced. The study of carcinogenesis will also lead to the understanding of the causes of cancer now considered to be spontaneous.

THE CHEMISTRY OF CANCER TISSUES

From the biochemical point of view the surprising characteristic of cancers is the uniformity of their behaviour. Different tumours resemble each other closely, although the tissues or organs from which these tumours are derived have very divergent and individual metabolic patterns. This generalization is illustrated by numerous examples in 'The Biochemistry of Cancer' by J. P. Greenstein (1954), a book which is invaluable to anyone interested in the subject. In considering the chemistry of tumours, Greenstein pointed out how 'every normal cell, except possibly some rudimentary relics, carries on a specific and unique function . . . the particular tissue is metabolically (as well as morphologically) differentiated'. Different tissues and organs can be recognized from their metabolic and chemical characteristics as well as from their morphological appearances. The idea that cancer cells possess a distinctive 'tumour metabolism' has often been discussed. There is no

doubt that tumours have a relatively high rate of glycolysis (production of lactic acid from glucose) as first discovered by Warburg (1930), but the retina and muscle (under conditions of work) have still higher rates of glycolysis. Even in this characteristic, which is often considered to be peculiar to cancer tissue, the malignant cell has a median or 'undifferentiated' activity. In comparison with most normal tissues from which neoplasia are derived, however, the malignant growths have high rates of glycolysis. On the other hand, if the tissue from which a tumour arose possessed some specific enzymic activity, this is usually lost in the transformation of the normal into a malignant cell. Thus, the liver synthesizes urea from ammonia but it is unusual for hepatomas to be able to carry out this process. There are, of course, exceptions to this generalization, such as the pancreatic tumours which produce insulin, the carcinoids which secrete serotonin and the adrenal growths which elaborate active adrenal hormones.

One difficulty in comparative biochemistry is the lack of homogeneity of tissues. Normal and malignant tissues contain varying proportions of different cells, and tumours contain variable proportions of necrotic or dead cells. In spite of this, some general biochemical properties of cancer are clear. These include the relatively high concentration of deoxyribonucleic acid, the high glycolysis, the low respiratory quotient (0.75 to 0.9) found by Dickens and Simer (1930), and the lack of ability to carry out synthetic processes, except for those concerned with growth, such as synthesis of protein and nucleic acids.

Some writers have considered that the difference between normal and cancer tissues lies in the defective respiration of malignant cells. Warburg (1955) has claimed that substances which induce cancer do so because they damage respiration and so cause a 'tumour metabolism' which leads to cancer. The quantitative data on tissue respiration show that values expressed as Q_{O_2} vary from three (for pancreas) to thirty-one (for retina) for non-malignant tissues and from five (for some sarcomas) to twenty (for a mouse skin carcinoma). These figures do not show tumours to be deficient in respiratory activity, but that they have average values for this characteristic. The argument that cancer is caused by inhibition of respiration is not in agreement with the facts. Of the many known agents which induce cancer in animals, only urethane is an inhibitor of respiration and urethane induces tumours in doses which are much less than those which have any measurable effects on respiration. One odd property of tumour respiration is that it is depressed in the presence of glucose. This phenomenon, known as the Crabtree effect, is probably due to the inhibition of fatty acid oxidation but its significance is not clear.

Investigations of the last decade into tissue metabolism have shown that many of the cellular enzymes are enclosed in organized particles, such as microsomes, mitochondria and nuclei, all of which can be separated from homogenized tissues by centrifugation. The mitochondria isolated from tumours differ from those isolated from normal tissues such as liver in that

they uncouple oxidative phosphorylations. In this way the tumour mitochondria reduce the efficiency or utilization of the energy of respiration. The effect may be due to the tumour mitochondria being more easily broken than are mitochondria of non-malignant tissues (Emmelot and Bos, 1957).

Although malignant tumours often have no particular biochemical functions except growth, the growth rates of tumours vary over a very wide range (at least one-hundredfold). On the other hand, the rates of the energy-yielding processes of metabolism (respiration and glycolysis) are very similar (Boyland and Boyland, 1939). This must mean that the slow-growing tumours are much less efficient in utilizing chemical energy for the synthetic processes of growth than are the faster growing neoplasms.

CARCINOGENESIS

The reviews published in the *British Medical Bulletin* last year on the study of 'Causation of Cancer' show that progress has been rapid in this field during the last decade. The outstanding feature is perhaps the wide variety of the compounds and agents, which can cause cancer; these range from what are probably purely physical agents such as implanted films of plastics, through the ionizing radiations, the alkylating agents (derived from mustard gas) and many dyestuffs to the aromatic amines and polycyclic hydrocarbons (Boyland, 1952).

The first successful experiments in experimental carcinogenesis, carried out by Japanese workers, showed that coal tar would induce cancer on the skin of mice or rabbits. Using this test the late Sir Ernest Kennaway and his colleagues fractionated the active material from coal tar and isolated the hydrocarbon, 3:4-benzopyrene. This carcinogen has since been detected in soot, in polluted air of towns and in tobacco smoke. Many polycyclic hydrocarbons were synthesized by J. W. Cook and his colleagues so that we have reasonably complete knowledge of the relationship between chemical structure and carcinogenic activity in compounds of this type.

At the same time Japanese investigators found that the feeding of the azo dyes, butter yellow (4-dimethylaminoazobenzene) or *ortho*aminoazobenzene, to rats induced liver cancer. Many compounds of this type have been tested in American laboratories and again a great deal is known of structural requirements of molecules in this series. Some of these azo dyes were used extensively as food dyes before the nature of the hazard was recognized. The colouring agent, butter yellow, was probably the first intentional food additive to be recognized as carcinogenic. Since its discovery, however, a number of food dyes such as light green and some other food additives, including the synthetic sweetening agent, 'dulcin' (4-ethoxyphenylurea), have been found to induce cancer in laboratory animals. Such substances are not allowed to be added to food in this country even (as in the case of light green) if the carcinogenic action has been demonstrated only by injection.

Many carcinogenic compounds produce biological effects similar to those

produced by ionizing radiations. Such effects are called radiomimetic and, as cancer is caused by radiations, carcinogenesis can be considered as a radiomimetic action. The compounds which show most radiomimetic effects are the vesicants, mustard gas and nitrogen mustards and their derivatives, some of which are not vesicant. The fact that x-rays can produce blisters on the skin is of interest in this respect. The ionizing radiations and many radiomimetic substances produce the two different effects of inducing cancer and of controlling the growth of tumours and so of being useful in the treatment of the disease. Ionizing radiations, the nitrogen mustards and many other carcinogens produce specific damage to the chromosomes of dividing cells and increase the incidence of mutations. They also have profound effects on deoxyribonucleic acid (DNA) which is an important constituent of chromosomes and probably carries the inherited characters of the cell and individual. The actual chemical mechanism by which the DNA is changed is probably different with radiations, with the mustard type of compound and with other carcinogens. Mustard gas, the nitrogen mustards and related compounds can react chemically with ionized groups by introducing an alkyl residue; they are therefore alkylating agents. Their effect on DNA is probably produced by reaction with either the acid groups or the purine rings of the nucleic acid molecule. On the other hand, ionizing radiations split water into free radicals of hydrogen and hydroxyl. The hydroxyl radicals so produced can oxidize the purine rings or other parts of the nucleic acid.

Although the ionizing radiations such as x-rays are physical carcinogenic agents, they probably act by the chemical mechanism of liberating free radicals within the cell. But there are some substances which appear to be purely physical carcinogens—no satisfactory explanation of their action on a chemical basis having been proposed. Examples of agents of this type are the plastic materials 'bakelite', cellophane and the chemically inert polyfluoroethylenes which, when implanted in the subcutaneous tissue of rats, usually induce local sarcomas (Oppenheimer *et al.*, 1956). The effect appears to be dependent upon the size of the implanted sheet of material rather than on the chemical nature of the substance used. Thus tumours of this type have been seen following implantation of sheets of the metals, silver or gold, of natural materials including ivory and of fibres of asbestos but not by powered synthetic polymers. Whether this type of carcinogenesis is of any significance in regard to cancer in man is not known.

The divergent types of agents which can produce cancer suggest that there is a wide field of investigation in finding ways in which exogenous or environmental and possibly endogenous carcinogenic stimuli can be avoided.

CHEMOTHERAPY OF CANCER

The substances used in the treatment of cancer and leukæmia include hormones, alkylating agents (i.e. derivatives of mustard gas), antimetabolites and antibiotics.

The first effective chemotherapy of human cancer was the treatment of prostatic cancer by œstrogens introduced by Huggins, Scott and Hodges (1941) and by Haddow, Watkinson and Paterson (1944), which is still the most effective form of cancer chemotherapy. Although the mechanism of action is not completely understood, the effect is probably due to inhibition of the pituitary. Œstrogens are also effective in the control of breast cancer and in this case the action is almost certainly due to inhibition of pituitary function. Some patients with mammary cancer benefit from androgen therapy, but there is no satisfactory explanation for the result in these cases.

The use of nitrogen mustards, which are chemically alkylating agents, in therapeutics began during the last war. Experiments on animals and accidental exposure of personnel had shown that the vesicants, either mustard gas or the nitrogen mustards, had a leucopenic action. Following this, American and British workers tried nitrogen mustards in the treatment of leukæmia and related diseases. Good results were obtained in Hodgkin's disease and these compounds, HN2(methyl *bis*(β-chloroethyl) amine) and HN3(*tris*(β-chloroethyl)amine), are still used in the control of lymphadenopathies and leukæmia. The nitrogen mustards have rather violent side-effects and must be administered intravenously. Examination of many hundreds of mustard derivatives has resulted in drugs which can be given by mouth, have less side-effects and are more specific in action.

One group of alkylating agents has cyclic ethyleneimine groups in place of open chain β-chloroethyl groups. These include triethylene melamine (tretamine); used in lymphatic diseases. Others are triethylene phosphoramide and triethylene thiophosphoramide (thiotepa). The latter compound is not only effective against leukæmia and lymphadenopathies but also in some other forms of cancer, particularly ovarian tumours. Other types of nitrogen mustard have the active *bis*(β-chloroethyl)amine group attached to an aromatic nucleus. One compound of this type is 4-*bis*(β-chloroethyl) amino phenyl butyric acid (chlorambucil), which is most useful in the control of lymphocytic leukæmia. Another aromatic nitrogen mustard is *bis*(β-chloroethyl amino)phenyl alanine (the British melphalan or Russian sarcolysine) which is claimed to control seminomas of the testis. Another interesting development of a mustard type compound is 1:4-dimesyl glycol (busulphan), which has a specific action on myeloid cells, and is now widely used in the treatment of chronic myeloid leukæmia. When used in suitable doses it has little ill effect and often leads to improvement in the condition of patients. The biochemical basis of the action of these alkylating agents is not completely understood; they probably react chemically by alkylating the purines or phosphoric-acid residues of the cellular nucleic acids.

The first successful antimetabolite compounds were the folic acid antagonists, aminopterin and methyl aminopterin (methotrexate). Folic acid is necessary for biological synthesis of purines in the transfer of 'single carbon units'. Some folic acid antagonists are able to control acute leukæmia. Another drug of value in prolonging life in acute leukæmia is the

purine antagonist, 6-mercaptopurine (mercaptopurine). Both the anti-folic acids and the antipurines interfere with nucleic acid synthesis. These drugs are used in conjunction with steroid hormones in cases of acute leukæmia. Whereas the mean survival time of children with acute leukæmia before the advent of these drugs was three months, the mean survival when the drugs are used is now in the order of twelve months.

Of the hundreds of antibiotics which have been tried in experimental cancer, actinomycin D has found clinical application in treatment of lymphadenopathies. In the United States enormous numbers of crude and refined fermentation products are being tested against animal tumours in the hope of discovering effective drugs.

Experience with the known cancer chemotherapeutic compounds indicates that they are active against one type of cancer rather than against cancer in general. One of the difficulties is that tumours rapidly develop drug resistance, but it is hoped to overcome this by using multiple synergistic therapy when sufficient drugs are available.

SUMMARY

Investigation of the comparative chemistry and biochemistry of cancer tissues has not revealed any specific qualities of cancer cells. Tumours usually have average values for chemical constituents and metabolic processes reflecting their undifferentiated nature. In many respects tumours resemble other growing tissues.

Many types of carcinogenic compounds are now recognized and in some of these, the polycyclic hydrocarbons and the aromatic amines for example, we have considerable knowledge of the relationship between chemical structure and biological activity. With some carcinogenic agents, such as the mustard derivatives and ionizing radiations, recent work has given some indication of a possible mode of action.

Substances used in the chemotherapy of cancer and leukæmia include hormones, antimetabolites, alkylating agents (i.e. substances derived from nitrogen mustard) and antibiotics. There is hope of controlling the disease by the use of combined or synergistic therapy.

References

Boyland, E. (1952): *Cancer Res.*, **12**, 77.
——, and Boyland, M. E. (1939): *Biochem. J.*, **33**, 618.
British Medical Bulletin (1958): **14**, no. 2.
Dickens, F., and Simer, F. (1930): *Biochem. J.*, **24**, 1301.
Emmelot, P., and Bos, C. J. (1957): *Brit. J. Cancer*, **11**, 148.
Greenstein, J. P. (1954): 'The Biochemistry of Cancer', 2nd Edition, Academic Press, New York.
Haddow, A., Watkinson, J. M., and Paterson, E. (1944): *Brit. med. J.*, **ii**, 3393.
Huggins, C., Scott, W. W., and Hodges, C. V. (1941): *J. Urol.*, **46**, 997.
Oppenheimer, B. S., *et al.* (1956): *Cancer Res.*, **16**, 439.
Warburg, O. (1930): 'The Metabolism of Tumours' (translated by F. Dickens), London.
—— (1955): *Strahlentherapie*, **34**, 42.

VIRUSES AND CANCER

By P. R. PEACOCK, M.B., B.S., F.R.F.P.S.
Director, Cancer Research Department, Royal Beatson Memorial Hospital, Glasgow

As this is a highly controversial subject, it is well to define the terms of reference. For the purpose of this discussion I take 'cancer' to mean any proliferation of cells that would be diagnosed as malignant by an experienced pathologist. By 'virus' I understand a particulate agent having nucleic acid as an essential part of its structure and capable of replication within a susceptible living cell for which it may act as a specific pathogen. The nucleic acid component may be either ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) and is usually associated with a protein component.

Certain malignant tumours and leucoses of animals have been experimentally propagated in series by particulate matter of subcellular size extracted from the corresponding tumour and there is no reason to doubt that they are caused by specific viruses, but such tumours constitute a very small minority of those that have been investigated. The advent of electron microscopy has made it possible to see characteristic particles in fixed and dried preparations of cells known to contain the specific viruses of many diseases of plants, animals and bacteria. Although in the hydrated condition, in which they exist in living susceptible cells, the appearances presumably would be different, they are sufficiently constant to allow valuable deductions to be made about the intimate structure of viruses. The bacteriophages which present one of the less complicated virus host cells relationships have now been studied in greater detail under experimental conditions. There is no doubt that some viruses are specific extrinsic causes of some types of cancer in several species of animal but it does not follow that they have an origin independent of the susceptible cell in which we recognize their presence, in the sense, for example, that pathogenic bacteria or protozoa have an independent existence.

LEUKÆMIA IN FOWLS

In 1908, Ellermann and Bang showed that leukæmia of the fowl could be transmitted either by cells or by cell-free plasma. It is well known that Rous described a sarcoma that arose spontaneously in a fowl and that he was able to transmit it to closely related birds first by cell grafting (1910) and later by cell-free filtrates (1911).

There was nothing in the histological or cytological appearances of these neoplastic diseases to suggest that they differed essentially from leukæmia or sarcoma in mammals in which infectivity was not demonstrable. Further examples of infective or filterable sarcoma in fowls continued to be reported

from many parts of the world. One of these sarcomas, originally described by Fujinami and Mamoto (1911), was transmitted not only to fowls but eventually also to ducks in which the histological type was just like that in the fowl (Fujinami and Hatano, 1929). Subsequent work with the Rous sarcoma has shown that the virus of this tumour can infect pheasants (Andrewes, 1932), guinea fowl and turkeys (des Ligneris, 1932), and ducks (Duran-Reynals, 1942), causing in all the same histological picture. Some peculiar features, however, have been associated with such experiments which may have deep significance. Duran-Reynals (1940) showed that in very young chicks or ducklings the virus induces a hæmorrhagic disease characterized by multiple and fatal hæmorrhages due to destructive lesions of the walls of the blood vessels, and without evidence of neoplasia. Oberling and Guerin (1933) found that blood from leukæmic (erythroblastic) fowls, if mixed with glycerin and kept in the refrigerator for some weeks, could cause sarcoma when injected intramuscularly and this type of polyvalent action was confirmed by others. An obvious suggestion was that more than one virus may be involved or, alternatively, that the type of lesion depends upon the cell infected. Although both explanations are compatible with the facts, more recent work, notably by Beard (1957), has shown clearly that myeloblastosis and erythroblastosis of chickens are due to two distinct but serologically related viruses which can be distinguished by the ability of the virus of myeloblastosis to hydrolyse adenosine triphosphate and the inability of the virus of erythroblastosis to do so. Nevertheless, the two viruses are morphologically indistinguishable and antigenically similar in serological studies. This point is of great importance when we consider the interpretation of morphological evidence about virus-like particles in tumour cells or extracts. In the present state of our knowledge virus morphology tells us nothing about pathogenicity.

Although the erythroblastic and myeloblastic leukæmias are transmissible by specific viruses they do not behave as acutely infectious diseases in nature. On the other hand, visceral lymphomatosis, which is a contagious disease transmitted through the eggs and excreta of infected birds, is less easily transmitted by cell-free filtrates. This is one of the paradoxes often encountered in cancer research. The situation has been elucidated by epidemiological studies such as those of Burmester (1957). It is now established that the virus of visceral lymphomatosis is carried by many apparently healthy birds and indeed it seems probable that the virus is capable of a non-pathogenic saprophytic existence which ensures its survival. As a philosophical digression one might consider that the production of disease is as disastrous for the pathogen as for the diseased host, often leading to their mutual destruction. The saprophytic state offers the best prospect of survival for viruses as for more complex organisms. Disease is a disaster for all concerned, but perhaps it serves to ensure the constant selection of resistant mutants.

Failure to appreciate this state of affairs might lead one to suppose that

the demonstrable presence of virus-like bodies in cells necessarily implies that they are pathogens. When examining a lesion, whether neoplastic, inflammatory or degenerative, it is tempting to suppose that any virus-like bodies present are of etiological significance. Yet we are well aware that the presence of bacteria in a lesion is no guarantee that they are its essential cause. Morphological evidence must therefore be interpreted no less cautiously in the case of viruses than in the case of more easily identified organisms. The viruses of myeloblastic and erythroblastic leukæmia have been isolated in a sufficiently pure state to be identified as the essential causes of these two neoplastic diseases. Morphologically the particles resemble other known animal viruses, but even with the best resolution of electron microscopy nothing characteristic of a neoplastic virus has been identified.

In the case of the many manifestations of lymphomatosis in the fowl the morphological evidence for virus etiology is less reliable than the evidence from epidemiological and experimental transmission techniques. The mesoblastic tumours of spontaneous origin, like the Rous No. 1 and Fujinami sarcomas and the Mill Hill 2 endothelioma, although undoubtedly transmissible by cell-free extracts which contain the respective viruses, have yielded little morphological evidence of viral etiology. After laborious search in tissue cultures and in thin sections of such tumours, Oberling and his colleagues (Bernhard *et al.*, 1953) have found and recorded occasional groups and clumps of individual virus-like particles in association with neoplastic cells generally extracellular, although in two-dimensional electron micrographs the interpretation of position is not always possible. The first morphological evidence for the presence of virus in Rous sarcoma was presented by Claude, Porter and Pickles (1947) who illustrated virus-like bodies in the peripheral part of some sarcoma cells. All who have studied this problem agree that the majority of sarcoma cells seen in section by electron microscopy do not show virus bodies, but this may be due to chance, as many hundreds of sections would be required to reconstruct each individual cell which might contain only a few or even a single virus particle. Recently, Epstein (1958) has obtained more convincing evidence of a quantitative association between the presence of virus bodies as shown by electron microscopy and infectivity of Rous sarcoma extracts treated with a fluorocarbon preparation, arcton 63. As more evidence becomes available no doubt in time the morphological evidence will be more certainly interpreted, but at present it seems prudent to assume that not all of the virus-like bodies seen in electron micrographs of tumour preparations are of etiological significance.

MOUSE MAMMARY CANCER

So far we have considered only tumours of mesoblastic origin which are sometimes difficult to distinguish histologically from some chronic inflammatory lesions. The reticuloses, leukoses and leukæmias are subject to the

same consideration. Most pathologists, however, would agree that carcinoma of whatever origin is unequivocally neoplastic. Evidence for viral etiology of carcinoma is therefore of greater theoretical interest.

One of the first successful attempts to transmit a tumour experimentally was made by Moreau (1894) who grafted mammary tumours from mouse to mouse, but noticed some surprising results. He observed that, although the grafts grew at the site of inoculation, similar tumours sometimes arose at other sites even in the absence of a tumour at the site of injection. He evidently considered that this might be due to some kind of infection because he tried to transmit the disease by feeding mice on mammary tumour, but his experiments became confused by the individual enterprise of the mice, which devoured the wooden partitions which separated them, and interbred. In the resulting families mammary cancers occurred in some females but the pedigree relationships were not known. Moreau came very near to establishing the infective nature of this type of mouse cancer but it was only in 1933 that the mechanism of transmission was elucidated by the staff of the Jackson Memorial Laboratory, and more specifically by Bittner (1936, 1957).

The basis for the explanation of the etiology of mammary cancer in mice was the establishment of homozygous strains with a known incidence of mammary cancer as one of the selected characteristics. Several characters might go together, for example C_3H mice have wild agouti colour, whilst RIII mice are white and in both cases there is a high spontaneous mammary cancer incidence (80 per cent.). In contrast, C57 black mice have a very low mammary cancer incidence (under 2 per cent.). The association with colour is incidental. If the mammary cancer incidence was determined genetically then reciprocal hybrids between high and low cancer strains (e.g. C57 x C_3H and C_3H x C57) should yield similar results, but this was not found in practice. When the mother belonged to a high cancer strain the female progeny had the same high cancer incidence. When the mother belonged to the low cancer strain, the female hybrids had a low mammary cancer incidence. The difference was clearly not chromosomal in origin and was therefore referred to as an extra-chromosomal factor, but as this term is ambiguous, it was fortunately dropped.

Foster nursing showed that the milk was the vehicle in which transmission occurred and the agent is generally called the 'milk factor', or the 'mammary tumour agent' (MTA). Clearly both male and female progeny must absorb the MTA virus from their mother, if it is present in her milk, yet in nature mammary tumours only occur in the females. Lacassagne (1932), however, showed that young male mice of high cancer strain, when given large doses of female hormone 'folliculine' (œstrone had not yet been identified) developed mammary cancer. This illustrated an important factor in determining the evolution of this type of cancer. It also drew attention to hormone dependence in the case of mammary cancer in mice, a phenomenon which had already been demonstrated by Beatson in 1896 in the

human subject, but it must be emphasized that there is no corresponding evidence for a mammary tumour agent in the human or indeed in any other species than the mouse.

Moreover, late in life (over 1 year) mice even of some low cancer strains may develop mammary cancer unassociated with the mammary tumour agent. Such tumours may be transplantable experimentally but contain no demonstrable virus. Mammary cancer can also be induced in mice of any strain by methylcholanthrene, and these induced cancers do not depend upon the presence of the mammary tumour agent. Generalization must therefore be avoided, even in regard to one histological type of cancer.

Abundant experimental evidence has accumulated to show that the mammary tumour agent is particulate and that it is carried by high cancer strain mice in other tissues than the breast without causing neoplasia or any other lesion. Under these conditions it is a saprophytic virus. Andervont (1952) has shown that wild mice can carry the mammary tumour agent and there is thus evidence that this type of cancer has a natural mode of propagation compatible with the survival of both the host species and the virus. This is the type of equilibrium which makes for survival and there is every reason to suppose that such mammary cancer has existed in mice at least throughout this century and probably much longer. In contrast, the type of mammary cancer induced by methylcholanthrene must be considered as a new experimental disease for which there may be no naturally occurring counterpart.

LEUKÆMIA IN MICE

The other types of cancer that commonly occur spontaneously in mice are lymphomatosis, hepatoma and papillary adenocarcinoma of the lung. All are being studied experimentally, and liver and lung cancer have been induced by chemical carcinogens but have not been shown to have a virus etiology. Under experimental conditions, however, lymphatic leukæmia in C_3H mice of Bittner's strain seems to be transmissible by a subcellular factor, presumably a virus, to new-born mice less than 16 hours old (Gross, 1951). In the course of his studies Gross (1953) has shown that in addition to leukæmia the injected mice develop carcinoma of the parotid glands.

In attempting to confirm the transfer of leukæmia reported by Gross, Stewart independently observed parotid gland tumours in five out of 14 mice inoculated with leukæmic extracts when less than 8 hours old, but did not report them at the time, awaiting the results of repeated experiments. In 1955 she reported neoplasms of the parotid gland and adrenal medulla in C_3H mice injected with cell-free filtrates of leukæmic organs of AKR mice. Very recently the same group at the National Cancer Institute have reported the induction of neoplasms in hamsters (Eddy *et al.*, 1958) and in rats (1959) following inoculation with tissue culture fluid from AKR mouse leukæmia. The agent is called SE polyoma virus.

The etiology of these tumours is less clearly established than is that of

the mammary cancers but intensive work is proceeding and further elucidation may be anticipated. Enough is known to suggest that this is another example of cancer with a complex etiology in which a virus plays an essential part.

SKIN CANCER IN RABBITS

In 1915, cancer was induced in the ears of rabbits painted with coal tar by Yamagiwa and Ichikawa and this is generally taken to be the starting point for experimental carcinogenesis by chemical agents. Pure polycyclic hydrocarbons, such as 3,4-benzopyrene, methylcholanthrene, and 9,10-dimethyl-1,2-benzanthracene, will induce papilloma and keratinizing squamous carcinoma in the ears of rabbits although in this species histologically malignant carcinoma may retrogress spontaneously for unknown reasons.

In 1933, Shope described infectious warts occurring in wild cottontail rabbits in Iowa and was able to transmit the disease either to cottontail or to domestic rabbits by glycerinated extracts of the warts. The subsequent history of this disease under experimental conditions is instructive. In cottontails it runs a benign course as a rule although cancer may develop after a year or more of benign growth. In the domestic rabbit the disease begins as a benign wart but tends either to regress or to grow progressively into an invasive carcinoma. Rous and Kidd (1938) studied such tumours intensively and amongst other experiments showed that when rabbits' ears were painted with methylcholanthrene and this was followed by intravenous injection of Shope papilloma virus, then the skin tumours rapidly evolved into carcinoma. The virus, however, could not be recovered from the carcinoma even though for years there was immunological evidence of its persistence in serially grafted tumours (Rous and Kidd, 1940). Eventually even this evidence became negative although the carcinoma Vx2 continued to be transplantable by cell grafts.

As non-neoplastic viruses grow well in a variety of tumour cells under experimental conditions, as shown by Rivers and Pearce (1925) in the case of the Brown-Pearce transplantable carcinoma of rabbits in which vaccinia virus or virus III could be carried as a passenger, the persistence of the Shope papilloma virus in Vx2 carcinoma might be only an example of virus adaptation to a saprophytic state in a tumour cell. There is no doubt, however, that the Shope papilloma virus can initiate a new growth which may eventually become malignant without any other deliberately introduced carcinogen being involved.

ONCOLYTIC VIRUSES

The early work of Levaditi and Nicolau (1922, 1923) on a neurotropic strain of vaccinia virus which grew well in epithelial neoplasms in mice was followed by many other examples of non-neoplastic viruses growing in tumour cells either saprophytically or with demonstrably damaging action on the host cells. In 1940, Andrewes found that the Shope benign infectious

fibroma of rabbits accidentially infected with virus III regressed prematurely but a transplantable sarcoma RS1 similarly infected grew progressively. The convenience of being able to maintain virus strains in tissue cultures of tumour cells naturally led to a great expansion of this type of experiment, from which it became evident that some viruses show oncolytic properties.

Moore (1957) recently reviewed her own and others' work on projects designed to develop therapeutically useful virus strains for cancer treatment. Although this is a most attractive line of work it must be said that so far no safe and effective treatment has been evolved. One of the difficulties is to find an oncolytic virus for any particular tumour which is not also fatal or dangerous to the host. Whilst this difficulty is serious in animal experiments, it is far greater in human subjects. It would be necessary to grow the human tumour successfully in tissue culture (by no means an easy task in most cases), to test it with a range of viruses in the hope that one or more would prove oncolytic for the tumour, and then to administer a dose of virus which would destroy all the tumour cells *in vivo* without killing the patient. Clearly the practical difficulties are great, but not necessarily insurmountable.

DISCUSSION

From the examples of virus-induced cancer that have been described it will be evident that more than one virus can cause cancer and that very different histological types of cancer in several species of animal can be caused by viruses. No-one disputes these facts. Is it possible from this evidence to evolve a theory that would cover the etiology of all types of cancer in all species? Here there is no agreement. Undoubtedly plausible theories can be evolved based on virus etiology but not on a single virus type. There is no evidence that the viruses of the Rous sarcoma and the mouse mammary tumour agent are immunologically similar, and even within the mesoblastic fowl tumour group the viruses of the Fujinami sarcoma, Rous sarcoma and Mill Hill 2 endothelioma are distinct, and the elegant demonstration of biochemical differences between the viruses of erythroblastosis and myeloblastosis by Beard has already been noted. More than one distinct virus can cause sarcoma in fowls but viruses cannot be recovered from many transplantable fowl sarcomas (Murphy and Sturm, 1941; Peacock, 1946). Moreover, all the other types of virus-induced cancer can be compared with chemically induced or spontaneously occurring tumours of similar histogenesis, but in which no etiologically associated virus is demonstrable.

Morphological evidence for the presence of viruses in some tumours is proved by electron microscopic studies but their etiological significance is debatable. Further theorizing in the present state of knowledge is an exercise in philosophy. For those who enjoy weighing the pros and cons it should be mentioned that we know nothing about the origin of viruses although epidemiological evidence shows that the acutely infectious virus diseases have existed as long as recorded history, whereas many of the

chemical carcinogens used extensively in cancer research are of known and recent origin. There is no reason to suppose that the chemical carcinogens, β-naphthylamine or 2-acetylaminofluorene, exist in nature, and methylcholanthrene, though chemically related to bile acids, has never been demonstrated as occurring in nature; 3,4-benzopyrene, however, is often produced when organic matter is burned with incomplete oxidation and must have existed in atmospheric pollution in all civilized communities for many centuries at least.

Saprophytic viruses undoubtedly exist and under suitable circumstances might become pathogenic. In attempting to explain spontaneous cancer in man and in other species these and many other factors must be borne in mind. It is possible that viruses may eventually be used therapeutically as oncolytic agents in clinical medicine.

References

Andervont, H. B. (1952): *Ann. N.Y. Acad. Sci.*, **54,** 1004.
Andrewes, C. H. (1932): *J. Path. Bact.*, **35,** 407.
—— (1940): *Ibid.*, **50,** 227.
Beard, J. W. (1957): *Tex. Rep. Biol. Med.*, **15,** 178.
Bernhard, W., Dontcheff, A., Oberling, C., and Vigier, P. (1953): *Bull. Ass. franç. Cancer*, **40,** 311.
Bittner, J. J. (1936): *Science*, **84,** 162.
—— (1957): *Tex. Rep. Biol. Med.*, **15,** 211.
Burmester, B. R. (1957): *Ibid.*, **15,** 540.
Claude, A., Porter, K. R., and Pickles, E. G. (1947): *Cancer Res.*, **7,** 421.
des Ligneris, M. J. A. (1932): *Amer. J. Cancer*, **16,** 307.
Duran-Reynals, F. (1940): *Yale J. Biol. Med.*, **13,** 77.
—— (1942): *Cancer Res.*, **2,** 343.
Eddy, B. E., Stewart, S. E., Young, R., and Burroughs Mider, G. (1958): *J. nat. Cancer Inst.*, **20,** 747.
——, ——, Stanton, M. F., and Marcotte, J. M. (1959): *Ibid.*, **22,** 161.
Ellermann, V., and Bang, O. (1908): *Cbl. Bakt.*, **46,** 595.
Epstein, M. A. (1958): *Brit. J. Cancer*, **12,** 248.
Fujinami, A., and Hatano, S. (1929): *Gann*, **23,** 67.
——, and Mamoto, K. (1911): *Ibid.*, **5,** 13.
Gross, L. (1951): *Proc. Soc. exp. Biol. Med.*, (*N.Y.*), **78,** 342.
—— (1953): *Ibid.*, **83,** 414.
Jackson Memorial Laboratory Staff (1933): *Science*, **78,** 465.
Lacassagne, A. (1932): *C.R. Acad. Sci.* (*Paris*), **195,** 630.
Levaditi, C., and Nicolau, S. (1922): *Ibid.*, **86,** 928.
——, —— (1923): *Ann. Inst. Pasteur*, **37,** 443.
Moore, A. E. (1957): *Tex. Rep. Biol. Med.*, **15,** 140.
Moreau, H. (1894): *Arch. Méd. exp.*, **6,** 677.
Murphy, J. B., and Sturm, E. (1941): *Cancer Res.*, **1,** 609.
Oberling, C., and Guerin, M. (1933): *Bull. Ass. franç. Cancer*, **22,** 326.
Peacock, P. R. (1946): *Cancer Res.*, **6,** 311.
Rivers, T. M., and Pearce, L. (1925): *J. exp. Med.*, **42,** 523.
Rous, P. (1910): *Ibid.*, **12,** 696.
—— (1911): *Ibid.*, **13,** 397.
——, and Kidd, J. G. (1938): *Ibid.*, **67,** 399.
——, —— (1940): *Ibid.*, **71,** 787.
Shope, R. E. (1933): *Ibid.*, **58,** 607.
Stewart, S. E. (1955): *J. nat. Cancer Inst.*, **15,** 1391.
Yamagiwa, K., and Ichikawa, K. (1915): *Mitt. med. Fak. Tokyo*, **15,** 295.

HORMONES AND CANCER

By O. H. PEARSON, M.D., and C. P. RHOADS, M.D.

From the Sloan-Kettering Institute, Memorial Center, New York City

THE relationship of endocrine factors to the initiation and subsequent growth of experimental neoplasms in animals has been under extensive study during the past decade. The evidence for a role of hormones in tumorigenesis in experimental animals is impressive. Neoplasms of the anterior pituitary, adrenal cortex, ovary, testis, mammary gland, uterus and vagina, lymphoid organs, liver, prostate gland and the cutaneous tissues have been induced by alterations in the endocrine environment. The exact relationship of these observations to the development of human cancer, however, is not clear. There is no clear-cut evidence that hormones are carcinogenic in man. Nevertheless, the experimental neoplasms present convenient models for study and there may be no fundamental biological dissimilarity between animal and human neoplasms.

HORMONE DEPENDENCE

One of the most interesting developments in the study of animal neoplasms is the concept of 'hormone dependence'. The same endocrine alterations which are necessary for the induction of tumours have been found to be at least contributory, and in some cases essential, for the continued growth of the neoplasm. An example of this type of neoplasm is the thyrotrophic pituitary neoplasms produced in mice by thyroidectomy (Furth, 1955). Pituitary tumours induced by deprivation of thyroid hormone are initially transplantable only to athyroid recipients. These are 'conditional' or 'dependent' neoplasms. In the thyroidectomized host the growth of the tumours is progressive, but if thyroid hormone is supplied, the tumours regress and disappear. During the course of transplantation through new hosts, but not in the original host, the neoplasms acquire the capacity to grow in hosts with functioning thyroid glands and are then 'autonomous'. In the study of models of this type, Furth postulates a sequence of changes from a normal cell to hyperplasia, to dependent tumour, to autonomous tumour still responsive to hormones, and finally to full autonomy. Both autonomous and dependent tumours can metastasize. Dependent tumours can be arrested by restoring to normal the specific regulatory mechanism which was disturbed.

In man, there is a high incidence of cancer involving organs which are under direct endocrine regulation: i.e. the breast, uterus, ovaries and prostate. Although the relation of hormones to the origin of these cancers is unknown, the role of hormones in their subsequent growth is of considerable theoretical and practical importance.

CANCER OF THE BREAST

Beatson, in 1896, was the first to demonstrate 'hormone dependence' of cancer, at a time when very little was known about hormones as such. His demonstration, that removal of the ovaries from pre-menopausal women with advanced breast cancer resulted in temporary regression of the cancer

		Remissions		Failures
		>6 months	<6 months	
Per cent.		37.4	16.4	46.2
Remission (months)	Mean	12.4	4.1	—
	Median	10.0	4.0	—
Survival (months)	Mean	22.0+	10.2	6.3
	Median	15.0 (1/25 still living)	8.0	4.0

TABLE I.—Results of adrenalectomy or combined oöphorectomy and adrenalectomy in 67 patients with metastatic breast cancer (Lipsett *et al.*, 1957).

in some instances, indicated that the growth of such neoplasms was at least partially dependent upon the endocrine environment of the host. It has subsequently been shown that the tumour regression observed following oöphorectomy is due to withdrawal of the major endogenous source of œstrogens.

Oöphorectomy is one of the optimal modalities for the palliative treatment of pre-menopausal patients with metastatic breast cancer. In a recent study, 44 per cent. of these patients obtained objective remission of their disease for an average period of 14+ months. The reason for the failure of 56 per cent. of the patients to obtain benefit from castration is presumed to be that the cancer was either initially non-œstrogen-dependent, or by the time treatment was instituted it had undergone adaptation and lost its dependence upon œstrogens. The response to oöphorectomy has prognostic value because most of the patients who obtain benefit can obtain further improvement from additional endocrine therapy, whereas those who fail to improve are unlikely to benefit from further endocrine therapy. In the post-menopausal patient, oöphorectomy will occasionally produce a regression of the cancer, but the incidence of improvement is so low that this modality of therapy alone is not recommended. Although the ovaries may continue to produce some œstrogens after the menopause, their contribution to the total œstrogen production may not be sufficient to produce a significant alteration in œstrogen levels following ablation of these glands.

Adrenalectomy will induce regression of metastatic breast cancer in some patients who have previously been castrated. Similarly, combined ablation of ovaries and adrenal glands in post-menopausal patients with metastatic breast cancer will induce objective improvement comparable to the results

obtained from oöphorectomy alone in pre-menopausal patients. The results of these procedures in one series of patients are summarized in table I. The adrenal cortex is known to be a source of endogenous œstrogen production, and there is presumptive evidence that adrenalectomy induces improvement in patients with metastatic breast cancer by withdrawal of

		Remissions		Failures
		>6 months	<6 months	
Per cent.		42.0	14.0	44.0
Remission (months)	Mean	16.5+	3.8	—
	Median	12.0 (3/37 still in remission)	3.8	—
Survival (months)	Mean	24.5+	9.3	5.6
	Median	23.0 (8/37 still living)	8.0 (All dead)	5.0 (All dead)

TABLE II.—Results of hypophysectomy in 89 patients with metastatic mammary cancer (Pearson and Ray, 1959a).

œstrogens. Thus, pre-menopausal patients with breast cancer who fail to benefit from oöphorectomy, rarely, if ever, obtain benefit from adrenalectomy, whereas patients who obtain remission from oöphorectomy may obtain further improvement from adrenalectomy.

Total hypophysectomy has been performed in patients with metastatic breast cancer to determine whether there might be additional endocrine factors in, or mediated by, the pituitary which can influence the course of this disease. Hypophysectomy performed after oöphorectomy and adrenalectomy has produced further significant improvement in some patients, but the incidence and duration of beneficial results in a small series of patients do not seem to warrant carrying out both of these ablative procedures. The results of hypophysectomy are being compared with the results of adrenalectomy to assess the potential superiority of hypophysectomy. The results of hypophysectomy in one series of patients are presented in table II. Although the average duration of remissions is 4+ months longer in the hypophysectomy series than in the adrenalectomy series, this difference is not statistically significant at present. In one setting, the results of hyophysectomy appear to be superior to those of adrenalectomy. In pre-menopausal patients who obtained a beneficial response from oöphorectomy, hypophysectomy induced a higher incidence of remissions than adrenalectomy (table III). This difference is statistically significant at the 5 per cent. level.

Administration of *œstrogen* has failed to induce reactivation of tumour growth in five patients who had hypophysectomy-induced remissions, whereas after oöphorectomy-induced remissions, œstrogens readily pro-

duced reactivation of tumour growth. This suggests that in the absence of the pituitary, œstrogen does not stimulate tumour growth, and that some factor from, or mediated by, the pituitary is essential to permit œstrogen stimulation of tumour growth. The nature of this supposed factor is still obscure.

The use of *androgens and œstrogens* in the palliative treatment of breast cancer is well established. It is also apparent that both of these steroid hormones can produce acceleration of tumour growth in some cases. Pre-

Castration remissions	Adrenalectomy remissions	Hypophysectomy remissions	Percentage
18	9	—	50
15	—	11	87

TABLE III.—Oöphorectomy response versus adrenalectomy and hypophysectomy responses in patients with breast cancer (Pearson and Ray, 1959b).

liminary studies of the effects of androgens and œstrogens after hypophysectomy suggest that these steroids lack both their stimulatory and inhibitory effects on the growth of mammary cancer in this setting. This would suggest that the action of these hormones on inhibiting tumour growth may be indirect, involving the endocrine glands.

Adrenal cortical steroids are also useful in producing short-termed palliative effects in patients with breast cancer. Because of the brief inhibitory effects of these steroids, other modalities of endocrine therapy are preferred in initiating treatment. Pharmacological doses of cortical hormones can produce tumour-inhibitory effects even after ablation of endocrine glands including the pituitary, suggesting that this hormone may produce direct catabolic effects on the tumour.

Future investigation of the endocrine treatment of breast cancer should include initiation of optimal treatment at earlier phases of the disease. If breast cancer is more dependent upon the endocrine environment in the earlier phases, then greater palliative results may be obtained with the institution of optimal therapy at this time.

CANCER OF THE PROSTATE

Orchidectomy and œstrogens produce worth-while temporary remissions in a high percentage of patients with prostatic cancer. Attempts to extend this palliation by adrenalectomy have, for the most part, been disappointing. Although significant remissions have been observed following adrenalectomy, the incidence and duration of the improvement have not been sufficient to recommend its routine use. Hypophysectomy is also being explored as a possible means of extending palliation in these patients. Preliminary observations indicate that worth-while benefit can be obtained in some patients, but further observations are needed before its usefulness can be assessed.

ENDOMETRIAL CANCER

Baker (personal communication) has recently reported that he has obtained temporary objective regression of metastatic endometrial carcinoma in seven of 15 patients with the use of progesterone. Remissions have been sustained for periods of from three months to four years. Progesterone was administered in doses of 1000 mg. a week. This observation suggests that growth of human endometrial cancer may also be at least partially dependent upon the endocrine environment.

LYMPHOMAS AND LEUKÆMIA

Adrenal cortical hormones will produce considerable temporary remissions in some patients with acute leukæmia, chronic lymphatic leukæmia and lymphosarcoma. The concept of 'hormone dependence', however, does not seem to apply to these tumours. The effects of cortisone on these tumours may be related to its lympholytic action.

HORMONE-PRODUCING TUMOURS

In both man and animals there have been extensive studies of tumours which produce hormones. Because of the great diversity of the qualities and capacities of neoplastic cells, few generalizations are possible concerning these studies. Cancer of endocrine organs may or may not retain the capacity to produce hormones, and the capacity of neoplasms to produce hormones is not necessarily related to its growth rate or invasiveness.

Steroid hormone excretion patterns have been extensively studied in patients with adrenal cortical carcinoma. Although marked quantitative alterations in the urinary excretion of hormone metabolites have been found, no qualitative change has been found which is characteristic of malignant cells. Hormone production by adrenal cancer may or may not be influenced by corticotrophin. Chemical agents capable of blocking hormone production may be active in malignant hormone-producing tumours without influencing the growth of the tumour. Thus, amphenone B has been shown to inhibit steroidogenesis in patients with adrenal cortical carcinoma without apparent effect on the growth of the neoplasm. Bergenstal and colleagues (personal communication) have recently demonstrated that an isomer of DDD can not only inhibit hormone production, but also induces regression of adrenal cortical carcinoma in man. Hormone production by malignant neoplasms is a useful index in the exploration of chemotherapeutic agents.

Another bizarre characteristic of malignant neoplasms is the occasional occurrence of the production of hormones, or the tripping off of excessive hormone production, which is not usual to the tissue of origin. Thus, high titres of urinary chorionic gonadotrophin have been found in patients with adrenal cortical carcinoma, breast carcinoma and malignant melanoma. An inadvertent finding that amethopterin suppressed the excretion of chorionic gonadotrophin in a patient with melanoma led Li and his colleagues (1956)

to explore the use of this antimetabolite in patients with choriocarcinoma. Remarkable regressions of widespread metastatic choriocarcinoma have been achieved with the use of amethopterin and other antimetabolites in women with this trophoblastic neoplasm.

Many other examples of the apparent ability of malignant neoplasms to acquire aberrant endocrine functions or possibly to incite inappropriate hyperfunction of endocrine glands are being recognized. Carcinoma of the kidney and lung may be associated with alterations in calcium and phosphorus metabolism, usually considered characteristic of hyperparathyroidism. Removal of the primary neoplasm has resulted in the return of calcium and phosphorus metabolism to normal, as though a parathyroid adenoma had been removed. Cushing's syndrome has been associated with a number of neoplasms other than the pituitary and adrenals, but in particular with oat-cell carcinoma of the lung. The carcinoid syndrome has been associated with metastasizing bronchial adenomas.

SUMMARY

The evidence for the role of hormones in tumorigenesis in experimental animals is impressive, but corresponding causal relationships in man are not apparent. Hormone dependence of human mammary and prostatic cancer is well established, and appropriate alterations of the endocrine environment afford effective palliative therapy for many of these patients.

Hormone-producing tumours provide the opportunity for studying the functional capacity of malignant neoplasms and the possible alterations of such functions during the life history of the cancer. So far, no qualitative change in hormone production has been found which is characteristic for malignancy. Hormone production by tumours provides a useful tool in evaluating potential chemotherapeutic agents.

The possibility that malignant neoplasms may acquire aberrant endocrine functions or incite inappropriate hyperfunction of the endocrine glands is suggested by the association of certain endocrine disorders with the existence of a neoplasm in some patients.

These studies were supported in part by grants from the National Cancer Institute of the National Institutes of Health, United States Public Health Service, the United States Atomic Energy Commission, the American Cancer Society, Inc., and the Damon Runyon Memorial Fund.

References

Beatson, G. T. (1896): *Lancet*, **ii**, 104.
Furth, J. (1955): *Recent Progr. Hormone Res.*, **11**, 221.
Li, M. C., Hertz, R., and Spencer, D. B. (1956): *Proc. Soc. exp. Biol.* (*N.Y.*), **93**, 361.
Lipsett, M. B., Whitmore, W. F., Jr., Treves, N. E., West, C. D., Randall, H. T., and Pearson, O. H. (1957): *Cancer*, **10**, 111.
Pearson, O. H., and Ray, B. S. (1959a): *Ibid.*, **12**, 85.
——, —— (1959b): 'Cancer', vol. 6, edited by R. W. Raven, London (in the press).

HEREDITY AND CANCER

By P. C. KOLLER, Ph.D., D.Sc.
Professor of Cytogenetics, Institute of Cancer Research, Royal Cancer Hospital

In general practice the doctor meets with a number of inquiries concerning the role of heredity in the causation of cancer. Patients whose close relatives have died of cancer are naturally concerned to find out if their chances of meeting a similar fate are greater than those of the community at large. Those of inquiring mind will ask why some heavy smokers live to a ripe old age, whereas others succumb to cancer of the lung. A good deal of publicity has recently been accorded to modern methods of the control of cancer in order partly to emphasize the value of early diagnosis and partly to relieve the distress of cancer patients. This publicity makes it increasingly important to compound suitable answers to the question indicated above.

HISTORICAL BACKGROUND

As early as the 17th century the physician, Hoffman, suggested that proneness to cancer might be inherited. He collected the histories of several families which showed a high frequency of the disease. Throughout the 18th and 19th centuries many similar pedigrees of families were published, mainly as curiosities (Wolff, 1907). Some of these pedigrees formed the basis of statistical investigations into the familial tendencies of the disease, but these studies were without any value because of the selective methods of compilation and lack of suitable control data. It is not surprising that owing to the unreliability and generally contradictory nature of these results most members of the medical profession inclined to dismiss heredity as an unimportant factor in the development of cancer, or as something that was beyond the reach of their remedies. Whilst this latter estimate is still true there is now a considerable body of information on the hereditary component of cancer that cannot be so easily dismissed.

EXPERIMENTAL STUDIES IN MICE

It is the customary practice in any investigation of heredity to consider the observed characteristics (= phenotype) of the individual as being the result of interaction between the inherited constitution (= genotype) and the environment. In the case of cancer the appearance of the disease is the particular aspect of the phenotype under study and the problem is to define what are the respective parts played by the genotype and the environment in its determination. This can be done either by comparing different genotypes in the same environment or subjecting the same genotype to differing environmental conditions.

By inbreeding mice for more than 20 generations, a great variety of

strains were established within which individual members have very similar genetical constitutions or genotypes. Many authors have recorded the spontaneous incidence of cancer in these mice which, it should be remembered, had been kept in very similar environments. The results were remarkably consistent. Each strain was found to have a characteristic incidence of a particular type of cancer. This was a strong indication of the existence of a genetically determined susceptibility to cancer (Heston, 1948; Grüneberg, 1952; Woolley, 1953; Koller, 1956). Table I illustrates for some inbred strains of mice the incidence of cancer and the average age at the onset of

Tumour	Strain	Tumour incidence in percentage	Average age of mice in months when tumour appears
Mammary gland	C3H	95	9
	RIII	90	16
	A	80	12
	DBA	65	12
	CBA	15	20
	Balb/C	1	24
	C57BL	0.5	22
Lung	A	85	14
	C57BL	0.5	18
Leukæmia	AKR	95	10
	C58	90	10
	DBA/2	40	12
	C57BL	20	18
	Stoli	1	16

TABLE I.—Tumour incidence in various strains of mice.

the disease. The experiments were carried further, and it was found that the onset of the disease could be accelerated and its frequency increased in susceptible strains if carcinogens such as benzpyrene, methylcholanthrene or x-rays were applied. Thus in A strain mice, which normally have an 85 per cent. incidence of lung cancer at 14 months, 1:2:5:6 dibenzanthracene, applied to the skin, increases the incidence to 100 per cent. and reduces the latent period to six weeks. In other strains of mice with lower susceptibility, carcinogens were found to have little or no effect. The experimental data force upon us the conclusions that in mice susceptibility to cancer is inherited and that different genotypes differ in their response to carcinogenic hazards.

Although these findings are no longer disputed, the exact Mendelian mechanism by which the predisposition to cancer is transmitted from parents to offspring, is not always clear. The general picture is that susceptibility is determined by a large number of genes each of small effect, but in certain cases, for instance lung cancer in A strain mice, it has been shown that only a few genes are involved. It is known also that a number of *non-*

genetic factors play a part in the etiology of cancer in mice, such as the filterable cytoplasmic agent in the development of mammary carcinoma in certain strains of mice. This agent should properly be regarded as an intimate environmental factor which, reacting with the genotype, makes it highly probable that tumours will arise.

HUMAN CANCER

The question is how the contributions of animal experiments can help us towards a better understanding of the respective roles of heredity and environment in the causation of cancer in man. Can the basic conclusions of experimental work with mice be applied directly? According to Heston, who carried out the most extensive investigation into the genetical basis of cancer in mice, the problem is 'no longer *if* cancer is inherited in man, but instead *how* cancer is inherited in man and *how* important are the genetic factors as compared with the various non-genetic factors in determining whether or not cancer will occur' (Heston, 1952).

SIMPLE AND OBVIOUS GENETIC CONTROL

Pedigree analysis of human material has revealed a few instances of the inheritance in a simple manner of a very high susceptibility to a particular type of tumour.

(a) *Retinoblastoma.*—Weller (1941) and Griffith and Sorsby (1944) investigated its incidence in families and found it to be determined by *one* dominant gene. Since retinoblastoma is nearly always fatal if not removed by surgery its sporadic reappearance is attributed to new mutations (see Koller, 1956).

(b) *Neurofibromatosis.*—Cockayne (1933) collected many family pedigrees and was able to show that the pattern of inheritance of neurofibromatosis suggested control by a single dominant gene.

(c) *Multiple polyposis.*—This precancerous condition was first investigated by Lockhart-Mummery (1925) and Dukes (1930, 1952). The study of 41 family pedigrees showed that polyposis of the intestine is due to one dominant gene. The average age of death due to malignant transformation of such polyps is 41 years whilst that for rectal cancer in the general population of England and Wales is 67 years.

(d) *Xeroderma pigmentosum.*—This condition, a general hypersensitivity of the skin to ultra-violet light, usually results in epidermoid carcinoma. Control of susceptibility can be attributed to a single recessive gene, located in the sex chromosome (see Koller, 1948).

These cases, in which the actual mode of inheritance is simple and obvious, are rare and are not representative of the more common types of cancer. Here the genetical control is likely on *a priori* grounds to be of a more complex nature similar to that found in the animal experiments. Suspecting this, two questions arise: How can human pedigree data give more precise

information? What part does the environment play in the development of tumours in man?

COMPLEX GENETICAL CONTROL

Before attempting to answer these questions it should be borne in mind that the normal methods of genetical analysis by controlled breeding experiments, are not applicable to man. Information must be gained by inference rather than directly. Family pedigrees are the main source of information. If the genetic constitution has a marked influence on the likelihood of an individual getting cancer, then families should be found in which an excessive number of close relations have cancer. The study of human pedigrees, however, is beset with difficulties. In many cases the cause of death two to three generations ago remains uncertain and cannot be recorded. The number of relatives of cancer propositi is often too small to give a statistically significant result. Furthermore, cancer being common in the population, the presence of several cancer cases in the same family does not necessarily mean the presence of a familial inherited predisposition; it may be due to chance alone. This possibility was mentioned many years ago by Bashford (1908). On similar lines Woolf (1955) calculated the number of cancer deaths which may occur according to the laws of probability in a hundred families of varying sizes in the State of Utah. His findings are illustrated in table II.

No. of deaths from cancer	Size of families					
	3	4	5	6	7	8
Nil	65	57	48	43	36	32
1	30	35	38	39	40	39
2	5	7	12	15	18	21
3	—	1	2	3	5	7
4	—	—	—	—	1	1

TABLE II.—The expected chance distribution of cancer deaths in 100 families of varying sizes (Woolf, 1955). (The expected numbers were calculated by the expansion of the binominal $N(p+q)^k$; probability value based on proportionate mortality rate due to cancer in persons over 20 years of age between 1946 and 1949 in the State of Utah, U.S.A.).

The most frequent shortcoming of genetical studies, however, is the lack of a suitable control group. The establishment of such a group, in which the members have the same environment, social, economic and cultural conditions as those of the cancer-group, is rarely, if ever, possible (Penrose *et al.*, 1948). Over and above all these difficulties lies the fact that cancer is not a single entity but a complex of many diseases. This has led to confusion in the past when a search has been made for a tendency to inherit cancer in general rather than susceptibility to a particular type of tumour. The more recent genetical investigations of human cancer have taken the various

factors just mentioned into consideration. The family pedigree studies now employ improved statistical methods and, in selecting the control material, more rigorous criteria are used. An impressive number of pedigrees has been collected and analysed by Lentz (1947) and Schintz and his collaborators (1948). The latter investigation covers more than 25,000 individuals and the pedigrees are followed through seven generations. In the compilation of family histories the emphasis is now on the occurrence of the same type of cancer in the same organs instead of the indiscriminate recording of all types of cancer. The investigations of carcinoma of the breast by Jacobsen (1946), Penrose *et al.* (1948), Macklin (1952), and Woolf (1955), of carcinoma of the uterus by Broebeck (1949) and Murphy (1952), and of carcinoma of the stomach by Gorer (1938) and von Verschuer and Kober (1940) all bear out this point.

Gorer (1938) and von Verschuer and Kober (1940) investigated the familial incidence of *gastric carcinoma* and concluded that susceptibility is genetically controlled. The predisposition, however, was found to be strictly site-specific. More recently, Woolf (1955) analysed the family pedigrees of 200 patients with gastric carcinoma and found 44 with carcinoma of the stomach among the 1,639 close relatives (mother, father, sister and brother). The number to be expected on the mortality rate of gastric carcinoma for the general population is 25, indicating that the risk is twice as great for relatives (particularly for the brothers, according to Woolf) to develop gastric carcinoma, as for those in whose family no members died from this disease.

Penrose and his colleagues (1948) concluded a survey in England on 510 *breast cancer* cases and compared the deaths from cancer in these families with cancer mortality rates in the general population. They found that 25 mothers and 23 sisters of the breast cancer patients died from cancer of the breast when 11 and 7 deaths were expected. It seems from the data that the risk of contracting breast cancer is three times higher for a sister of the proposita, than for another woman whose family had no death from carcinoma of the breast. Woolf (1955) analysed the families of 200 patients with breast cancer in Utah (United States) and arrived at the same conclusion as Penrose.

Pedigree studies of 200 patients with *carcinoma of the cervix* were carried out by Broebeck (1949) in Denmark. The female relatives of the propositæ had more cancer of the cervix than was expected according to the mortality rates in the general population. Murphy (1952) compiled the family histories in the United States of 201 uterine cancer patients and 215 controls, a total of some 6,445 individuals, and he also found a higher number of endometrial cancer in the close relatives than was expected.

The familial incidence of *leukæmia* was investigated by Videbaek (1947) in the Danish population. He obtained 209 leukæmic patients to serve as propositi, and collected 200 controls from various sources. According to

Videbaek's interpretation of the data, there is a predisposition to leukæmia, and this is associated with a tendency towards cancer in general. A critical examination of Videbaek's control group, however, has shown that it is not representative of the general population, as it contained only 73 per cent. of the expected cancer cases. A more recent study seems to suggest the presence of a hereditary predisposition to leukæmia in certain families (Videbaek, 1958).

The studies of these various investigators indicate that predisposition to gastric and breast cancer is more than a possibility. It was found that the risk of contracting cancer at these sites is 2 to 3 times higher for certain members of certain families, than the risk for members of those families in which no such cancer occurred. Although in these investigations attention has been paid to cancer at a particular site, only rarely has it been possible to effect comparison between the incidence of cancer of a particular histological type at one site. It remains to be seen in what way this analytical refinement will affect the present data.

It is important to note, however, that as yet no general predisposition to cancer has been revealed. Neither has a simple pattern of inheritance emerged from these pedigree data. It can therefore be inferred that many genes are involved in determining susceptibility to the common cancers. Although the presence of inherited cancer susceptibility in certain families is apparent, it must be strongly emphasized that genetical predisposition must not be looked upon as the sole etiological factor in the origin of cancer. The effect of environmental influences upon the susceptible genotype must be assessed. The studies of cancer incidence in identical twins and various racial groups permits this assessment.

TWIN STUDIES

Family pedigrees in which both twins are affected with cancer are available in the medical literature. Some cases in which cancer occurs concordantly, i.e. in both members of a twin-pair, are very striking indeed. Militzer (1935) reported a case in which both male members of monozygotic twins had identical symptoms and almost simultaneously developed gastric carcinomas which were symmetrically located in the stomach and even had the same histological features. Gorer (1938) found four pairs of monozygotic twins in which both members had leukæmia. Should we regard such instances as purely fortuitous, or should we consider them as strong evidence in favour of a genetic predisposition?

The largest systematic study of twins has been carried out in Denmark by Busk and his associates (1948). They collected 315 pairs of twins among 30,000 hospital cases, in which at least one member had cancer. By critical scrutiny Busk and his collaborators were able to make a final analysis of 185 pairs, 52 monozygotic and 133 dizygotic twins. Using the cancer risk in the general population as a basis of comparison, they calculated the expected

values for the number of times both twins should have been affected. According to this calculation five pairs out of 52 monozygotic twins were expected to have cancer in both members, and seven pairs were observed; for the 133 dizygotics, nine pairs were expected and seven pairs were found. When both members of a monozygotic pair were affected with cancer, the disease was found to be localized in the corresponding organs.

Gorer (1958) recently surveyed the occurrence of gastric carcinoma in several pedigrees of twins compiled by von Verschuer and Kober (1940) and Busk *et al.* (1948) and came to the conclusion that there is a strong genetic predisposition for gastric carcinoma. In this survey nine out of 19 monozygotic twins showed concordance and the tumours were gastric carcinoma in seven pairs! In the other two pairs, one tumour was in the stomach, the other in the intestine. The remaining 11 monozygotic twins had cancer only in one member. According to the tenets of genetics, identical monozygotic twins should have identical genotype; consequently, discordance, when only one member died from cancer, underlines the significance of the environmental influences over the genotype in the development of cancer. This fact is more clearly expressed in the survey of breast cancer incidence in monozygotic twins; out of the 17 pairs, only one was found to have breast cancer in both members, in the other 16 pairs only one of the twins was affected.

This brief review of studies of cancer incidence in monozygotic twins shows that the presence of predisposition does not decide the fate of an individual, it is the outcome of the environmental influences acting upon the genetic constitution. Further data are needed to show the exact nature of the environmental factors which reacted to produce cancer in one identical twin but not the other.

CANCER IN RACIAL GROUPS

The importance of environment in the development of cancer is shown clearly by the studies into the incidence of the same cancer in different racial groups (Steiner, 1954). Such investigations brought to light some facts which initially seemed to suggest that genetically determined racial differences for certain cancer may exist. The best known case is that of primary carcinoma of the liver. It is common in the Bantu tribes of Africa, and was attributed to a heritable predisposition. This belief has been modified by Davies (1955) who has shown that it is environmentally conditioned and follows dietary deficiencies in early childhood. Davies demonstrates that cancer of the liver in American Negroes was no higher than that in the white population. Similarly, the startling differences observed in the incidence of penile cancer between the Hindu and Moslem population of India should be considered in cultural rather than genetical terms; the low incidence in Hindus can be related to circumcision in early life. A slightly different case is that of skin cancer. It was found that negroids and other

races with pigmented skin have less cutaneous cancer than the white races. The difference has a genetic basis, but the genetic control is indirect, being exercised by the genes which determine the degree of pigmentation in the skin, and hence the protection of the epidermal cells from sunlight.

Although many data have been accumulated on racial differences in the incidence of cancer their significance is difficult to assess. Steiner (1954) considered the rather cosmopolitan population of Los Angeles. He found that the Mexican elements had a higher incidence of tumours of the lung, larynx, gall-bladder and bone. The Negroes showed a higher incidence of ovarian tumours. The Japanese population had an abnormally high frequency of tumours of the stomach and liver, and the Chinese of the nasopharynx. The frequencies of tumours in the home countries of these various types of immigrants was shown to be similar to that found in Los Angeles. Ostensibly the data show significant racial differences with a very real hereditary component, but the immigrants carry with them to their new environment most of the customs and dietary habits which prevailed in their homeland. In such circumstances how is it possible to differentiate between genetic and environmental factors in the incidence of tumours?

CONCLUSION

A summary has been made of our knowledge of the inheritance of susceptibility to cancer in mice and men. It has been pointed out that in both organisms the mode of inheritance is usually complex, involving a large number of genes. In man it has been shown that there is probably a strong inherited predisposition to cancer in certain sites, particularly the stomach and breast and to a less extent the cervix and uterus. Incidence of tumours at other sites has been insufficiently investigated from the hereditary point of view. It remains to be seen, for instance, whether it will be possible to demonstrate a hereditary component to cancer of other parts of the body such as the lung and the bladder. The evidence from studies of twins lays more stress on the importance of the environment in the etiology of cancer and shows how in most cases identical susceptible genotypes do not meet with exactly the same environments. Racial differences in the frequency of incidence of cancer are not well documented and it is not easy to partition the hereditary and environmental components of susceptibility. But again the stress must be laid on environmental factors, particularly in considering such a genetically heterogeneous population as the human race.

The data so far are in many ways imperfect and inadequate. They do, however, permit an estimate of the risks for members of a family in which cancer has appeared in certain forms. Whether such information is used in response to direct inquiries from relatives of propositi is a debatable matter. The main use would be in ensuring vigilance in situations where the cancer susceptibility is likely to be high, so that early diagnosis would be the rule and exposure to any carcinogenic hazard could be reduced to a minimum.

It is essential that the hereditary component of susceptibility to cancer should be taken into consideration by the general practitioner.

References

Bashford, E. (1908): *Lancet*, **ii**, 1508.
Broebeck, O. (1949): Universitetsforlaget, Aarhus.
Busk, T., Clemmesen, J., and Nielson, A. (1948): *Brit. J. Cancer*, **2**, 156.
Cockayne, E. A. (1933): 'Inherited Abnormalities of the Skin and its Appendages', London.
Davies, J. N. P. (1955): *J. nat. Cancer Inst.*, **15**, Suppl., 1637.
Dukes, C. (1930): *Cancer Rev.*, **5**, 241.
—— (1952): *Ann. Eugen. (Lond.)*, **17**, 1.
Gorer, P. A. (1938): *Ibid.*, **8**, 219.
—— (1958): *Ann. N. Y. Acad. Sci.*, **71**, 1189.
Griffith, A. D., and Sorsby, A. (1944): *Brit. J. Ophthal.*, **28**, 279.
Grüneberg, H. (1952): 'The Genetics of the Mouse', The Hague.
Heston, W. E. (1948): *Brit. J. Cancer*, **2**, 87.
—— (1952): *Amer. J. hum. Genet.*, **4**, 314.
Jacobsen, O. (1946): 'Heredity in Breast Cancer', Copenhagen.
Koller, P. C. (1948): *Brit. J. Cancer*, **2**, 149.
—— (1956): *Cancer*, **1**, 335.
Lentz, O. (1947): *Arb. Statsinst. exp. Ther. Frankfurt*, 45.
Lockhart-Mummery, P. (1925): *Lancet*, **208**, 427.
Macklin, M. T. (1952): *Proc. nat. Cancer Conf.*, **2**, 1074.
Militzer, R. E. (1935): *Amer. J. Cancer*, **25**, 544.
Murphy, D. P. (1952): 'Heredity in Uterine Cancer', Cambridge, Massachusetts.
Penrose, L. S., Mackenzie, H. J., and Karn, M. N. (1948): *Brit. J. Cancer*, **2**, 168.
Schintz, H. R., Cocchi, U., and Neuhaus, J. (1948): *Arch. Klaus.-Stift. Vererb.-Forsch.*, **23**, 1.
Steiner, P. E. (1954): 'Cancer, Race and Geography', Baltimore.
Stephens, F. E. (1954): *Amer. J. hum. Genet.*, **6**, 60.
Verschuer, O. von., and Kober, E. (1940): *Z. Krebsforsch.*, **50**, 5.
Videbaek, A. (1947): 'Heredity in Human Leukæmia and its Relation to Cancer', Copenhagen.
—— (1958): *Acta path. microbiol. scand.*, **44**, 372.
Weller, C. V. (1941): *Cancer Res.*, **1**, 517.
Woolf, C. M. (1955): *Univ. Calif. Publ. publ. Hlth*, **2**, 265.
Wolff, J. (1907): 'Die Lehre von der Krebskrankheit von den ältesten Zeiten bis zur Gegenwart', Jena.
Woolley, G. W. (1953): In 'The Physiopathology of Cancer', edited by F. Homburger and W. H. Fishman, London, p. 171.

THE CYTOLOGICAL DIAGNOSIS OF MALIGNANT DISEASE

By J. BAMFORTH, M.D., F.R.C.P., F.R.C.O.G.

Shepherd Research Fellow, King's College Hospital; Pathologist, Imperial Cancer Research Fund

CYTOLOGICAL examination as an aid to the diagnosis of malignant conditions is being used throughout the world on an ever-increasing scale. Two types of cytology may be recognized, exfoliative and non-exfoliative, although there is no sharp distinction between them. Cardozo (1954) defines 'exfoliative cytology' as the examination of cells that in a natural or artificial way become detached from tissue surfaces, whereas 'non-exfoliative cytology' refers to the examination of cells obtained by needle aspiration or drill biopsy in solid organs or tissue masses. The former deals with the examination of smears from secretions and excretions, in particular, the sputum, vaginal secretion, stomach washings, prostatic secretion, pleural and pericardial fluids. It is in exfoliative cytology that so much work has been done during the last ten to twenty years but increasing attention is being paid to non-exfoliative cytology, especially in relation to the diagnosis of biopsy material.

NON-EXFOLIATIVE CYTOLOGY

More than thirty years ago, Dudgeon began to use the cytological method for the examination of fresh tissues.

> The tissue removed at operation is incised and scraped with a sharp scalpel. The juice so obtained is smeared upon a glass slide, fixed *while still wet* in Schaudinn's fluid, stained with hæmalum and eosin and mounted in Canada balsam. Beautiful preparations are made by this simple technique.

The details of the cell nucleus and cytoplasm are more clearly shown than in paraffin sections. Dudgeon and Patrick (1927), and later Dudgeon and Barrett (1934) published articles giving an account of more than 1000 cases examined in this way. The diagnoses made from the examination of the smears compared favourably with those from paraffin sections. In order to become proficient in this technique it is necessary to become familiar with the appearances of normal and malignant cells as found in smears from various tissues and organs, and to compare and identify them with those found in the sections.

It was soon evident that this method of diagnosis was capable of wide application. It could be used instead of a frozen section in the course of an operation, as a rapid method for the examination of a doubtful breast tumour, or in the outpatient department in small lesions of the skin or mouth. Cytological diagnosis in certain skin lesions has been employed in this country by Haber (1954), who states that the method has been systematically used in Paris for some years. He found it particularly useful

in the diagnosis of tumours, bullous eruptions and virus diseases. The method was helpful when a quick preliminary diagnosis was requested and the patient refused biopsy, in the case of very old people, and when the lesion was difficult of access—for example at the corner of the eye, mouth or nostril. The differences in the appearances found in the smear of a basal-cell carcinoma (rodent ulcer) and a squamous-cell carcinoma are illustrated in figures 1 and 2.

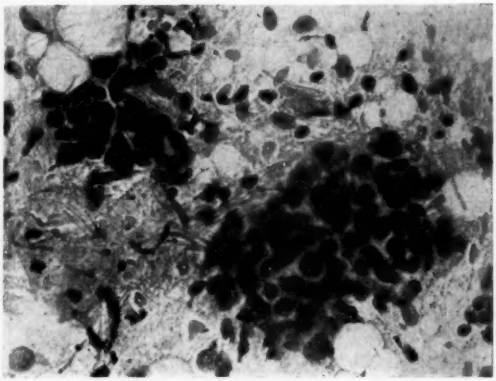


FIG. 1.—Smear prepared during life from a rodent ulcer. (x 410)

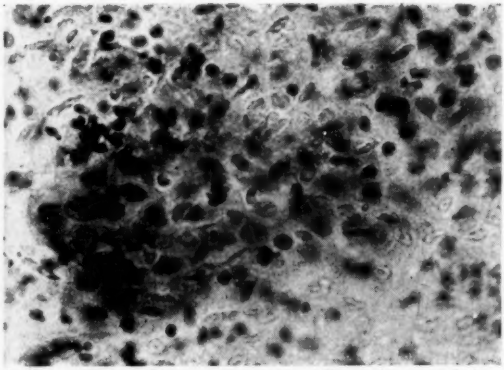


FIG. 2.—Smear from a squamous-cell carcinoma of the skin. Compare the appearances with those seen in fig. 1. (x 410)

A rapid method for the diagnosis of the different types of brain tumours is obviously desirable when considering the question of the treatment to be adopted. As long ago as 1937, Russell, Krayenbühl and Cairns described an adaptation of the wet-film technique of Dudgeon for this purpose. The fragments of brain and tumour tissue removed by a needle were spread upon a glass slide, fixed and stained in the operating theatre. Many types of brain tumour can be recognized by this procedure and the authors state that the diagnostic difficulties which arose were those found when using any histological method.

It is often desirable to take a biopsy at a particular spot in a bone or tumour by means of a syringe or drill; only a very small amount of material may be obtained, possibly of fluid consistency. The wet-film technique is admirably suited to this type of examination.

Biopsy of enlarged lymph glands is often practised and often gives valuable information when the question of malignant disease arises. Lymph gland puncture is preferred by some authorities but, in my opinion, it is

better that the whole gland be removed. When secondary carcinoma is present in the gland there is rarely any difficulty in making the diagnosis. The malignant cells as seen in the stained smears differ so much in appearance from the cells normally present that they are readily recognized. A smear from a supraclavicular lymph gland showing malignant cells derived from a primary cancer of the stomach is illustrated in figure 3. Hodgkin's disease is easily observed, provided the characteristic pathological changes are sufficiently developed in the gland, but the same difficulty may be found in histological section. In the absence of a blood examination it may be difficult to distinguish between lymphatic leukæmia and lymphosarcoma.

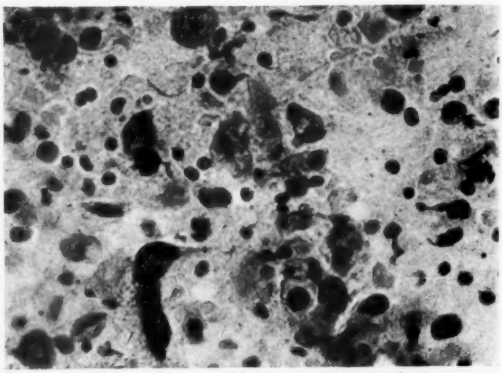


FIG. 3.—Smear from a biopsy specimen of a supraclavicular gland showing the presence of malignant cells —secondary to a primary carcinoma of the stomach. (x 410)

In the course of a radical operation for cancer it may be important to ascertain whether or not the regional lymph glands are involved by metastatic spread. Cytological examination is well adapted to solve this question. Way (1959) has made use of this method for some years in operations on carcinoma of the vulva; surgical procedure is modified depending upon the results obtained.

EXFOLIATIVE CYTOLOGY

The application of exfoliative cytology has increased considerably during the past few years. Experience has been acquired by cytologists in different parts of the world in searching for malignant cells in the sputum, vaginal secretion, pleural and pericardial fluids, stomach washings and in prostatic secretion. These procedures have acquired importance in diagnosis and will be further considered in this article. Attention is now being paid to the examination of smears from the nasal sinuses, the œsophagus, duodenal juice, large bowel, breast secretion, urine and cerebrospinal fluid, and increasing numbers of reports are appearing in the literature.

THE SPUTUM

There are numerous references in the literature to the finding of malignant cells in the sputum. Dudgeon and Wrigley (1935) were the first to report the results of a systematic examination of sputa in patients suspected of

having carcinoma of the bronchus. They succeeded in obtaining 68 per cent. of positive results in cases subsequently proved to be malignant. Precisely the same technique was followed as already described. The value of sputum examination has been confirmed by many workers throughout the world using a variety of staining methods. A wet-film methylene blue technique was devised by Schuster (1947), and modifications of it have been successfully employed by others (Jennings and Shaw, 1953). When it is remembered that about 25 per cent. of pulmonary neoplasms are beyond the reach of the bronchoscope, the definite finding of malignant cells in the sputum is important. The removal of a small piece of malignant tissue by bronchoscope may settle the diagnosis but in some cases none is found and bronchial washings are sent for examination. My results obtained with bronchial washings have been disappointing and compare unfavourably with those from sputum. Osborn (1958) has been very successful in examining aspirated bronchial mucus undiluted with saliva.

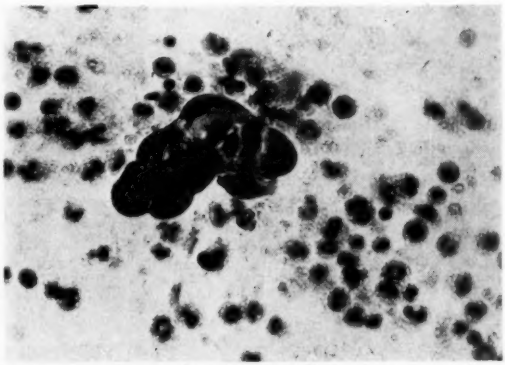


FIG. 4.—A clump of malignant cells in the sputum from a case of adenocarcinoma of the lung—confirmed at post-mortem examination. (x 410)

Three main types of malignant cells may be found in sputum, corresponding to oat-cell carcinoma, adenocarcinoma, and squamous-cell carcinoma. A group of malignant cells found in the sputum from a case of alveolar-cell carcinoma is shown in figure 4. Even the most experienced cytologist may obtain a small percentage of false positive results, but in my experience these are more likely to be due to cells wrongly considered to represent adenocarcinoma, which, especially in asthmatics, may occasionally be found in the sputum. In a few cases very small and early neoplasms may be discovered in the lung following a positive report on the sputum.

VAGINAL SECRETIONS

One of the most important advances in the early diagnosis of cancer was the introduction of the cytological method for the investigation of malignant disease of the female genital tract (Papanicolaou and Traut, 1943). This highly successful method has exercised a profound influence not only on the diagnosis of pathological conditions of the female genital tract, but on the use of exfoliative cytology in general. Considerable accuracy in diagnosis can be attained and Graham (1953) claimed that 90 per cent. of

cancer of the cervix and 70 per cent. of cancer of the body can be diagnosed by one vaginal smear. Papanicolaou's work has been amply confirmed by workers all over the world and an increasing number of centres for the detection of uterine cancer by the cytological method is being established both in this country and abroad.

All workers in this field are insistent that *cytological examination be regarded as an important* but *preliminary means of diagnosis*. If cells in the vaginal smear are reported as positive or 'suspicious' of malignancy, further investigation (biopsy or curettage) is considered essential. In this way, many early and unsuspected cases of malignancy have first been discovered: cases in which, in the absence of cytological examination, no biopsy would have been undertaken. Almost all have proved to be cervical carcinoma either of the early invasive or of the intra-epithelial non-invasive type. The latter condition, now usually termed 'carcinoma *in situ*', occurs also in many other regions of the body and is still a matter of great interest and speculation. When this lesion is first diagnosed in the uterine cervix the ultimate prognosis is problematical. This is an important consideration as an increasing number of these lesions is being identified. There appears to be no doubt that after a varying period of time (from a few months to twenty years), the lesion may evolve into a typical invasive cancer, and in about 30 per cent. of untreated cases this occurs within nine years. There is also evidence, however, that histologically similar lesions, after a varying period of time, may regress and finally disappear (Kottmeier, 1953; Petersen, 1955, 1956). A more extensive follow-up and further histological study of these cases are required but much time may pass before a better understanding of this lesion is obtained.

With a view to increasing the efficiency of the cytological diagnosis of carcinoma of the uterus, a number of changes in technique has been suggested. Ayre (1947) described a small wooden spatula for gently scraping the surface of the vaginal portion of the cervix, especially in the region of the squamo-columnar junction. A second film can thus be prepared for examination in addition to that from the vaginal pool. This method is much favoured by some authorities. As already indicated, the results obtained by most workers in carcinoma of the body of the uterus are not so good as in carcinoma of the cervix. Recently, greater accuracy has been claimed from the use of smears obtained by aspiration with a syringe from the uterine cavity (Hecht, 1952; Varangot *et al.*, 1954). This procedure could represent a definite improvement in technique but in any case in which carcinoma of the uterine body is suspected, dilatation and curettage should be preferred.

CARCINOMA OF THE STOMACH

The prognosis in patients suffering from carcinoma of the stomach is almost invariably bad. In the minority of cases in which radical excision is possible the recurrence rate is high. Few patients survive for five years. A small number of early cases has been described in some of whom the

growth is confined entirely, or for the most part, within the mucous membrane. These early lesions, often found in close proximity to a chronic simple ulcer, are divided into two types: carcinoma *in situ*, and superficial spreading carcinoma. The prognosis after operation appears to be rather better in these cases (Mallory, 1940; Stout, 1942).

The diagnosis of carcinoma of the stomach in its early stage is often difficult and may be impossible. Clinical symptoms may be indefinite; x-ray examination may sometimes reveal a change in the outline of the stomach, and gastroscopy may help, but in recent years cases have been reported in which cytology alone has been the means of diagnosis. Various techniques have been employed to obtain suitable specimens.

Preparations made from the aspirated contents after fasting overnight, followed by lavage of the stomach with normal saline or Ringer's solution, have yielded malignant cells in some cases. In order to dissolve the mucus, which is often present in large amounts, and to ensure better centrifugalization, papain (Rosenthal and Traut, 1951) or chymotrypsin (Van der Reis *et al.*, 1956) has been advocated. An abrasive balloon (Panico *et al.*, 1950) which can be rapidly inflated and deflated, or a brush (Ayre and Oren, 1953) to detach cells from the malignant area, has also been used. Work is still in progress. Considerable practice and experience are required, in both preparation and interpretation of the smears.

In this country, Schade (1958), using the simple lavage method advocated at the Vincent Memorial Hospital, has achieved considerable success. About 2,500 gastric cytological examinations have been made and 25 cases of carcinoma have been discovered by cytology when radiology and gastroscopy were negative. Schade diagnosed a number of cases in which the tumour was as yet entirely confined to the mucosal layers and no lymph node metastases were present. He found that the best material for cytology was obtained from cases of superficial spreading carcinoma when the malignant lesion was small. When the growth was large and ulcerated, cytodiagnosis was more difficult due to the presence of many organisms and inflammatory cells.

CARCINOMA OF THE PROSTATE

The clinical diagnosis of carcinoma of the prostate made by rectal examination is often unreliable. The serum phosphatase shows a normal level when the growth is confined within the capsule. When growth has taken place beyond the capsule, and especially when bone metastases are present, both the acid and the alkaline phosphatase are often, but not always, significantly raised. A diagnosis of carcinoma cannot be excluded unless every part of the prostate has been examined and therefore a negative biopsy, whether peri-urethral or perineal, is not necessarily conclusive. Herbut and Lubin (1947), and Peters (1950), were among the early workers to show the possibilities of cytology in the diagnosis of prostatic carcinoma. Fergusson and Gibson (1956) described in detail the method of obtaining a satisfactory specimen of prostatic secretion by massage, and reported an accurate diagnosis of 94.7 per cent. in a series of 40 cases of prostatic carcinoma. Unfortunately, in my own experience about one-third of the smears received from different sources did not contain sufficient prostatic epithelial

cells for critical examination. The quality of the smears obtained varies in different hands; the technique of massage appears difficult to acquire, and in scirrhous carcinoma it may be impossible to obtain a satisfactory specimen. With good smears cytological examination may be a valuable diagnostic aid.

FIG. 5.—Part of a 'cast' of malignant cells found in the secretion obtained following prostatic massage in a case of carcinoma of the prostate — see fig. 6. (x 410)

FIG. 6.—Photomicrograph of a section of the biopsy specimen from a case of prostatic cancer giving confirmation of the diagnosis made on the appearances in the smear—see fig. 5. (x 410)

In older subjects, innocent prostatic cells found in the smear after massage tend to occur in sheets and show considerable uniformity in size, shape and arrangement. The nuclei are equidistant from one another and the cytoplasm sharply defined at the periphery by the cell membrane, giving the appearance of mosaic work. In most cases malignant cells tend to occur in clumps and are crowded together with overlapping nuclei which are definitely enlarged in relation to the cytoplasm. These clumps often resemble renal casts (fig. 5).

Sometimes the crowding is not so marked but the nuclear and cytoplasmic changes found in malignant cells generally may be observed. The malignant cells themselves vary considerably in different cases; at the one extreme they may be large, resembling transitional cells; at the other, very small, resembling lymphocytes. By comparison with histological sections from biopsy or post-mortem material, different cell types may be established (Bamforth, 1958). See figures 5 and 6.

The patients who suffer from prostatic carcinoma are almost always of advanced age and in many cases no surgical procedures of any kind are undertaken. Follow-up obviously presents great difficulties. A comparison of the results obtained by cytological diagnosis with the evidence available from follow-up (in spite of the initial difficulty in obtaining suitable preparations in all the cases) shows that the examination of prostatic smears may be of value in diagnosing prostatic carcinoma.

PLEURAL, ASCITIC AND PERICARDIAL FLUID

The examination of pleural, ascitic and pericardial fluid for the presence of malignant cells may yield important information to the clinician. Some authorities have used paraffin sections but the cytologist prefers stained films made from the centrifuged deposit. The films are fixed while still wet and can be stained by hæmalum and eosin or by Papanicolaou's technique. Spriggs (1957), who has been very successful in the examination of serous fluids, used air-dried films stained by May - Grünwald - Giemsa. The cells seen in stained films are less shrunken and the cell details more clearly shown than in paraffin sections. Malignant cells in serous effusions may be derived from primary growths in many parts of the body. In my experience, in the great majority of cases the original tumour is located in the lung, ovary, breast, stomach, large intestine or lymphoid tissue. From a study of the various types of malignant cells seen in effusions it is often impossible to determine the site of the primary lesion. Foot (1954), however, showed that it is possible to diagnose the type and source of malignant cells with an over-all accuracy of about 70 per cent. It is important to realize that confusion may result from the presence of endothelial cells. In certain circumstances, for example in lung infarct, they may proliferate, become detached from the serosal surface and be present in large numbers in the fluid. They may become atypical in appearance and occur in clumps. In this way interpretation may be difficult, especially in some cases of adenocarcinoma in which the malignant cells may closely resemble mesothelial cells.

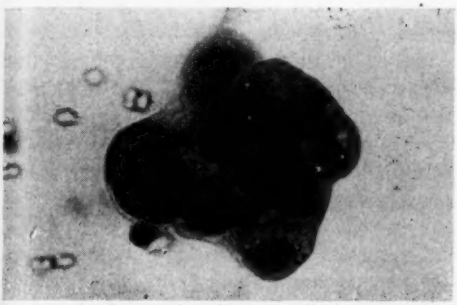


FIG. 7.—A clump of malignant cells in the pleural fluid from a late metastasis in a case of spheroidal-cell carcinoma of the breast. (x 550)

A clump of malignant cells in the pleural fluid due to recurrence of carcinoma of the breast is demonstrated in figure 7. The patient had a primary spheroidal-cell carcinoma of the breast removed at operation eight years previously.

CANCER CELLS IN THE BLOOD

It has long been accepted that cancer cells are present in the blood and during recent years increasing interest has been taken in evolving methods for their detection. Pool and Dunlop (1934) demonstrated the presence of malignant cells in the blood of 17 out of 40 patients by hæmolysing it with acetic acid and sectioning the remaining cells. Engell (1955) employed a similar technique but used saponin instead of acetic acid. Moore and his

co-workers (1957) separated the red cells by sedimentation with fibrinogen, centrifuged the supernatant plasma and prepared smears from the buffy coat which was found to contain the tumour cells. Engell found in patients with carcinoma of the rectum and colon that the chances of detecting cancer cells in the blood were considerably increased in the more dedifferentiated neoplasms. In Broders Grade II tumours, cells were found in 35 per cent. of cases; in Grade III, 78 per cent., and in Grade IV in 100 per cent. There was no definite alteration in the number of malignant cells in the venous blood before and after manipulation of the tumour. It is clear that improved technique in the detection of malignant cells in the blood, together with the possibility of establishing a consistent and reliable method of enumerating them, might yield much information regarding the efficacy of present and future therapeutic measures in the treatment of cancer.

References

Ayre, J. E. (1947): *Amer. J. Obstet. Gynec.*, **53**, 609.
——, and Oren, B. G. (1953): *Cancer*, **6**, 1177.
Bamforth, J., (1958): *Ann. Roy. Coll. Surg. Engl.*, **23**, 248.
Cardozo, P. Lopes (1954): 'Clinical Cytology', Leyden.
Dudgeon, L. S., and Barrett, N. R. (1934): *Brit. J. Surg.*, **22**, 4.
——, and Patrick, C. V. (1927): *Ibid.*, **15**, 250.
——, and Wrigley, C. H. (1935): *J. Laryng.*, **50**, 752.
Engell, H. C. (1955): *Acta chir. scand.*, suppl., 201.
Fergusson, J. C., and Gibson, E. C. (1956): *Brit. med. J.*, **i**, 822.
Foot, N. C. (1954): *Amer. J. Path.*, **30**, 661.
Graham, R. M. (1953): *J. Obstet. Gynæc. Brit. Emp.*, **60**, 483.
Haber, H. (1954): *Brit. J. Derm.*, **66**, 79.
Hecht, E. L. (1952): *N.Y. St. J. Med.*, **52**, 2745.
Herbut, P. A., and Lubin, E. N. (1947): *J. Urol.*, **57**, 542.
Jennings, R. C., and Shaw, K. M. (1953): *Thorax*, **8**, 288.
Kottmeier, H. L. (1953): 'Carcinoma of the Female Genitalia', Baltimore.
Mallory, T. B. (1940): *Arch. Path. Lab. Med.*, **30**, 348.
Moore, G. E., Sandberg, A. A., and Schuberg, J. R. (1957): *Ann. Surg.*, **146**, 580.
Osborn, G. R. (1958): In 'Cancer', vol. 3, p. 476, edited by R. W. Raven, London.
Panico, F. G., *et al.* (1950): *J. Amer. med. Ass.*, **143**, 1308.
Papanicolaou, G. N., and Traut, H. F. (1943): 'Diagnosis of Uterine Cancer by the Vaginal Smear', London.
Peters, H. (1950): *Cancer*, **3**, 481.
Petersen, O. (1955): *Acta radiol. Stockh.*, suppl., 127.
—— (1956): *Amer. J. Obstet. Gynec.*, **72**, 1063.
Pool, E. H., and Dunlop, G. R. (1934): *Amer. J. Cancer*, **21**, 99.
Rosenthal, M., and Traut, H. F. (1951): *Cancer*, **4**, 147.
Russell, D. S., Krayenbühl, H., and Cairns, H. (1937): *J. Path. Bact.*, **45**, 501.
Schade, R. O. K. (1958): *Brit. med. J.*, **i**, 743.
Schuster, N. H. (1947): In 'Recent Advances in Clinical Pathology', edited by S. C. Dyke, London, p. 316.
Spriggs, A. I. (1957): 'The Cytology of Effusions', London.
Stout, A. P. (1942): *Arch. Surg. (Chicago)*, **44**, 651.
Varangot, J., *et al.* (1954): *Amer. J. Obstet. Gynec.*, **68**, 474.
Van der Reis, L., *et al.* (1956): *Amer. J. med. Sci.*, **231**, 249.
Way, S. A. (1959): Personal communication.

CARCINOMA OF THE BLADDER

By A. W. BADENOCH, M.D., Ch.M., F.R.C.S.
Surgeon, St. Bartholomew's Hospital and St. Peter's Hospital for Stone

Cancer in the urinary bladder is not very common when compared with its occurrence in certain other parts of the body. Nevertheless, its importance is not to be judged by its numerical incidence, and there are several salient features which focus patients' attention on the occurrence of cancer in this region.

BIOCHEMISTRY

It has been known for a number of years that carcinoma of the bladder is found more frequently in certain chemical workers—dyestuff workers, aniline workers, and workers in the gas and tar distillery industries—than in the general population, and there is also evidence that it could occur in certain stages of rubber processing, especially under war-time conditions. It has therefore become a prescribed disease under the provisions of the National Insurance Act. Bonser and her associates in Leeds (1956) have shown that the carcinogens are certain intermediaries of aromatic amines which are activated after conversion to *ortho*-aminophenols. It is probable that in the chemical workers the aromatic amines are absorbed through the lungs, alimentary tract or the skin and ultimately reach the liver. There they are metabolized to *ortho*-phenols, which are carcinogenic, but these are immediately conjugated with sulphuric acid or glucuronic acid. These conjugates, which are non-carcinogenic, are excreted and concentrated by the kidneys so that their concentration is higher in the urine than elsewhere. The effective activity of the enzyme, β-glucuronidase, which hydrolyses the conjugates of *ortho*-phenols, is also high in urine, and these conjugates can therefore be more readily hydrolysed in the urine than elsewhere in the body.

As the tumours which occur in the bladder of chemical workers have similar histological characteristics to those found in the general population, Boyland and his associates (1955), working at the Chester Beatty Institute, suggested that cancer of the bladder in general may be due to the excretion of a carcinogen in the urine. They found (1956) that patients with bladder cancer excrete more 3-hydroxyanthranilic acid and 3-hydroxykynurenine. Subsequently, by employing the mouse bladder implantation technique they proved that each of these *ortho*-aminophenol derivatives—3-hydroxykynurenine, 3-hydroxyanthranilic acid and 2-amino-3-hydroxy-acetophenone—produces bladder tumours. It is significant that these substances which are known products of amino-acid metabolism are endogenous carcinogenic agents. Boyland (1958) has also suggested that as a result of some abnormality in tryptophan metabolism a conjugated 3-hydroxyanthranilic acid is excreted in increased amounts. The enzymes, sulphatase and β-glucuronidase, especially if present in increased amounts, will break

down this conjugate in the bladder and release the carcinogens which will then act on the bladder epithelium. The effect may well be increased if there is some obstructive factor at the bladder neck causing residual urine. Wallace (1956) has pointed out that a significant proportion of patients with carcinoma of the bladder have an obstructive factor and this may be one reason to explain the rather imponderable fact that the proportion of men suffering from carcinoma of the bladder is so much higher than of women.

It is not at present possible to influence the excretion of the conjugated aminophenol but the activity of β-glucuronidase can be reduced by the administration by mouth of saccharo-1→4-lactone.

PATHOLOGY

Carcinoma of the bladder as seen macroscopically can be grouped into two main patterns, papillary or pedunculated, and solid and sessile. Cuthbert Dukes, in 1955, prepared a classification of tumours of the bladder for the Institute of Urology, and this is used by the hospitals attached to the Institute and fairly generally throughout this country. It is of great practical value since it can be applied to biopsy specimens, is important in deciding the correct line of treatment, is helpful in prognosis and can afford some measure of comparison between different lines of treatment. Tumours can be arranged into six fairly well-defined groups:—

(1) Papilloma (benign)
(2) Differentiated transitional-cell carcinoma
(3) Undifferentiated or anaplastic transitional-cell carcinoma
(4) Squamous-cell carcinoma
(5) Adeno-carcinoma
(6) Other varieties, which include mesothelial tumours.

A papillary tumour does not infiltrate as readily as one which is sessile. A well-differentiated transitional-cell carcinoma invades slowly, a poorly differentiated tumour invades rapidly and metastasizes readily. Secondary deposits have been recorded in most organs of the body. Willis (1953) considers that bladder cancers deposit in heart muscle more readily than any other tumours. Lymphatic and blood-stream spread occurs with equal facility in transitional-cell tumour. Although areas of squamous-cell metaplasia can occur in a papillary tumour, a predominating squamous-cell carcinoma is always sessile and solid. It is locally invasive to a high degree, but seems to metastasize less readily and has less tendency to invade blood vessels than other types of carcinoma. Metastases, when they occur, are found in the local lymph glands and rarely is there visceral spread. Cooling (1958), in reporting a series of 150 post-mortem examinations on patients dying with carcinoma of the bladder, found that the lymph nodes were affected in 88 per cent. of cases, the liver in 51 per cent., the lung in 39 per cent., bones in 22 per cent., and the peritoneum in 13 per cent.

SYMPTOMATOLOGY

Hæmaturia.—By far the commonest presenting symptom of carcinoma of the bladder is blood in the urine. It occurs in over 90 per cent. of cases.

Always in the male, and usually in the female, it is easily recognized, gives rise to alarm and in most cases makes the patient quickly seek medical advice. The bleeding is almost always painless. It may be quite profuse or scanty and, except in the very rare circumstance of a clot retention of urine, always clears up spontaneously in a matter of hours or days. The male may notice that the bleeding is worse at the beginning or the end of micturition. The female may have some doubt as to whether the blood has come from the bladder or the vagina but, if it happens more than once, is nearly always able to resolve this doubt.

Frequency of micturition.—This is a common symptom associated with hæmaturia when due to infection. In carcinoma of the bladder, which is either out of control or infected, it is usual and distressing. It can, however, also be a presenting symptom of carcinoma. A lesion originating on the trigone or near the internal meatus may cause increased frequency before giving rise to hæmaturia. An uncommon form of transitional-cell carcinoma occurs with small multiple submucous foci, and this at first has the clinical course and cystoscopic appearance of a subacute or chronic cystitis. The urine is sterile and may or may not contain pus cells. On cystoscopy, the appearances are atypical: there are usually several small areas of reddened, œdematous, mucous membrane with some congestion of the bladder wall between the areas. In the differential diagnosis, a simple pyogenic infection and tuberculosis must be eliminated, and sooner, rather than later, a biopsy must be done when the diagnosis will be established.

Difficulty in micturition.—This can occur when the growth is situated near the internal meatus. It may occur if bleeding is severe enough to cause partial or complete clot retention.

Pain.—This is nearly always a late manifestation. Infection and phosphatic concretions will lead to pain on micturition and to strangury which may be extremely severe. Perivesical spread will cause neuralgia, often sciatic in distribution, from direct involvement of nerves or may cause bone erosion with severe lancinating pains.

THE DIAGNOSIS AND ASSESSMENT OF A BLADDER TUMOUR

The observation of hæmaturia by a patient always calls for urological investigation. If there has been increased frequency of micturition accompanied by pain, and especially if the pain occurs before the bleeding, the latter is due to infection or to irritation from a stone. A careful history will almost certainly indicate whether a bacteriological examination is the first step in investigation. All cases of painless hæmaturia, more especially if it is profuse and periodic, must have a full urological investigation to find the cause and especially to eliminate a tumour of the bladder or of the upper urinary tract. This investigation will include cystoscopy, excretion urography, a bimanual examination of the bladder under full anæsthesia and a biopsy of the tumour. Cystoscopy always demonstrates the presence of a carcinoma in the bladder. It may be, of course, that at a given time, a proper inspection is not possible

on account of excessive bleeding. Using an irrigating cystoscope, which is the pattern of examining instrument now in general use, the urologist is able at least to get a glimpse of the tumour. This will establish the diagnosis, but it is not enough. It is essential that the whole bladder should be examined, that the size and position of the growth be seen and accurately charted and that no further tumour be overlooked. The nature of the growth is often obvious on inspection. If it is pedunculated and the fronds regular, symmetrical and graceful, it is benign. If sessile, flat, ulcerated and ugly, it is malignant but there are many growths which are less definite than these.

FIG. 1.—Filling defect on right-hand side of bladder due to papillary tumour still in the mucosal stage.

In planning the most appropriate treatment, it is important to stage the spread of the tumour. Clinically, we recognize four stages: mucosal (fig. 1), muscular, perivesical and mobile (fig. 2), and perivesical and fixed (Dukes and Masina, 1949; Wallace, 1956; Badenoch, 1956). A bimanual examination may do more to help in assessing the stage of spread, than any other single manœuvre. It should be done under full anæsthesia.

If the growth cannot be felt, and provided the patient is of reasonable dimensions and is properly relaxed, then it is in the mucosal stage or stage I. If the growth can be felt to slip about between the rectal and suprapubic fingers, it is largely inside the bladder and again probably stage I. If it is felt as a small plaque, smooth to the rectal finger but firm and hard and yet mobile, it has spread into the muscle and is at least in stage II. If it is irregular to the rectal finger as well, but still mobile, it has spread through the muscle, is perivesical and has reached stage III. If it is fixed to the lateral wall of the pelvis, it is in stage IV.

FIG. 2.—Multiple filling defects from papillary tumours, two of which had reached stage III.

At the time of the cystoscopic examination under anæsthesia, a portion of the tumour should be removed for histological examination. Special forceps have been designed to facilitate this, the Lowsley and the Riches patterns being those most usually employed. If the growth is on the trigone or near the internal meatus, it may be easier and safer to use the resectoscope or the cold punch. Lastly, an intravenous pyelogram should always be done. This will show the state of the kidneys and ureters. Any dilatation or stasis in a

ureter, whose orifice is near a growth, suggests that the latter has infiltrated into the bladder wall. If the ureter is grossly dilated, or if the kidney on this side has ceased to function, there can be no doubt of the spread. Information may be given by the cystogram. All growths of any size give some sort of

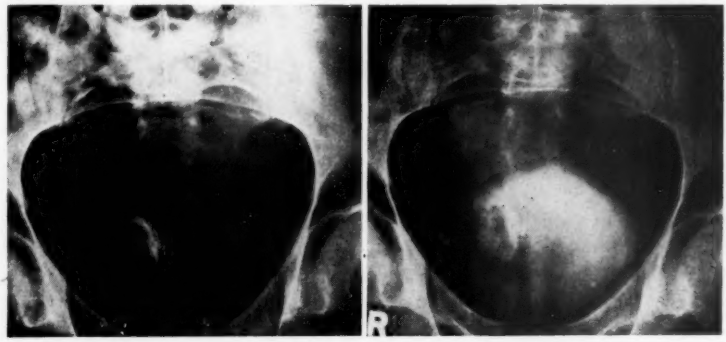


FIG. 3.—(a) Opacity seen in pelvis on plain film. (b) Opacity shows filling defect due to carcinoma of bladder, covered with phosphates.

filling defect in the bladder shadow (fig. 3). If the contour of the bladder wall is broken, and especially if a 'bite deformity' (fig. 4) is present the growth has infiltrated. If, on the other hand, there is a diminished density in the situation where the growth is known to be, this is much less likely and it may be benign. Flatus in the rectum and in a loop of sigmoid colon may suggest a filling defect but on cystoscopy this will not correspond with a growth.

CONTROL IN INDUSTRIAL CANCER

In workers in industries, where the hazard of bladder tumour is known to be increased, some method of early detection is essential. Obviously, a frank hæmaturia must have a complete urinary investigation, but in the absence of symptoms a routine check must be done, and the most important examination is that of the urine. A sample is collected at intervals, which must not be more than four months, in all workers exposed to risk.

Cooling (1958) reports the results in over 2000 persons examined at various factories over a period of six years. Wet smears of a centrifuged deposit of a freshly voided specimen are examined for erythrocytes and other cells. If these are seen a cytological search is made after the manner of Papanicolaou. As a result of positive findings, 111 men were cystoscoped and 80 new cases of bladder tumour were discovered. Of these, positive Papanicolaou smears were found in 73.

Unfortunately, employment of this method is not sufficiently accurate in the follow-up of patients who have had a tumour destroyed, and they will still require a cystoscopic examination at intervals for the rest of their life.

TREATMENT

Probably more changes have occurred in the last decade in methods of treating carcinoma of the bladder than elsewhere in the body. Surgical

extirpation alone has often proved unsatisfactory or unavailing, but many of the bladder lesions are radiosensitive. With the development of radioactive sources, there has been good reason to try their application, and results have been most encouraging. As elsewhere in surgery, a decision has to be made, not only as to the necessity for treatment but also as to its extent. Both surgery and radiotherapy, if successfully applied, may control the disease, but each and both may occasionally make the patient's life worse and death longer. The well-differentiated tumour is probably controlled as easily and more safely by surgery. The anaplastic or poorly differentiated tumour is almost always better controlled by radiotherapy. To some extent, these generalities are influenced by the stage of a growth.

FIG. 4.—Cystogram showing well-marked bite deformity from stage III carcinoma.

In stage I, when the tumour is confined to the mucous membrane, its complete destruction should be possible by local resection with a diathermy loop. Depending upon the accessibility, size and multiplicity of the tumour, this will be applied either endoscopically or after opening the bladder.

In stage II, when the tumour has invaded the muscle layer of the bladder wall, local resection may still be theoretically possible, but a more radical removal is almost certainly necessary. If the tumour is well differentiated and accessible, a partial or segmental cystectomy is usually employed. If poorly differentiated, accessible, and the patient a good surgical subject, again a segmental cystectomy may be performed. If the tumour is not easily accessible, and situated on the base of the bladder, or near the internal meatus, a variation of treatment is necessary. The well-differentiated tumour may require a total cystectomy, the poorly differentiated growth, radiotherapy. This will be in the form of an implant, either by gold grains, radon seeds (fig. 5), or tantalum wire. Each has its advantages, and its advocates. It may well be that the best result after implanting a radioactive source is in the stage II case, but usually the tumour has already been destroyed by diathermy excision or deep coagulation of the base.

The high-grade tumour which has reached stage III should be treated by beam irradiation from a radioactive source. With the use of the higher power super-voltage machines of 2 to 5 MeV, and more recently with the cobalt bomb, a considerable improvement in results has been obtained. So much so, that in all stage III anaplastic tumours, beam irradiation is now my first choice of treatment. In stage IV tumours it is the only choice.

There is still a place for total cystectomy (fig. 6). Ten years ago this was the fashionable line. The poor survival rates, together with the considerable

risks consequent upon infection and biochemical imbalance, have made us much more selective. A well-differentiated carcinoma too large or not accessible for segmental resection, multiple, well-differentiated growths where one or more have spread into the muscle, failure of irradiation or the occurrence of marked telangiectasis or necrosis, may all be indications for total cystectomy. Whether the diversion of urine will be into the sigmoid colon, into an ileal conduit or by cutaneous ureterostomy, will depend to some extent upon the surgeon, on the age, and on the physical wellbeing of the patient. On the whole, opinion favours a uretero-colic anastamosis, the nuisance value being balanced against the risk.

FIG. 5.—Filling defect from stage IV carcinoma, treated with radon seeds. *Note:* one seed has been carried by growth extending far outside bladder wall.

FIG. 6.—Extensive papillary carcinoma filling bladder (stage III). Most suitably treated by cystectomy.

PROGNOSIS AND RESULTS OF TREATMENT

Cancer of the bladder not only kills fairly quickly but usually kills in a most unpleasant and unkind way. Untreated, few if any patients survive for three years and, if the growth is perivesical and fixed when first seen, it is improbable that anything can be done to help the patient. At the mucosal stage, however, there is a very good chance of destroying the tumour and 75 per cent. are alive and well at the end of five years. This survival rate (Wallace, 1958) is not bettered by implanting a radioactive source. When the cancer has spread into the bladder muscle, there is not much to choose between different methods in published survival rates. Partial cystectomy appears to afford the best chance as 50 per cent. are alive at five years. The survival figures after interstitial implantation with tantalum wire are not apparently quite as good, being 37 per cent. There are, however, other factors to be considered. It is only fair to say that each case treated by partial cystectomy is carefully selected, both as to size and accessibility of the neoplasm and suitability of the patient to undergo a surgical procedure.

It was at first thought that intracavitary irradiation might be extremely

helpful when there were multiple papillary lesions but the side-effects and the results of the treatment with our present radioactive sources and methods are not good (Riches, 1958). For these lesions, each tumour should be destroyed meticulously and patiently by diathermy either through suitable endoscopic instruments or after opening the bladder. It should be emphasized that if these cases are to receive the optimum adequate treatment it is essential that the urologist should have been properly trained and should have at his disposal the necessary instruments. Too many bladders are opened unnecessarily and some are not opened in time. It is too early to judge the results of external irradiation on stage II and stage III growths, but the results after treatment by super-voltage machines, such as the linear accelerators and the cobalt bomb, are most encouraging. Even though results from segmental resection are quite good, irradiation therapy is especially applicable for the poorly differentiated or anaplastic carcinoma. The results after total cystectomy are not very encouraging (Riches, 1955), but in selected cases—and the operation is highly selective—much can be done to relieve the patient. In my opinion, a palliative cystectomy is never justifiable and it is doubtful whether the radical cystectomy introduced by Marshal (Marshal and Whitmore, 1956) has increased the survival rate. The technical difficulties of this operation are such that, except in the very thin patient, accuracy in dissection of glands cannot be obtained.

We are still far from controlling cancer of the bladder but with early and complete assessment, cooperation between urologist and radiotherapist, application of the best appropriate treatment, and careful follow-up, a longer survival with less discomfort can usually be effected than heretofore.

References

Badenoch, A. W. (1956): *The Practitioner*, **177**, 267.
Bonser, G. M., *et al.* (1956): *Brit. J. Cancer*, **10**, 539.
Boyland, E., (1958): In 'Tumours of the Bladder', edited by D. M. Wallace, Edinburgh, p. 98.
——, Wallace, D. M., and Williams, D. C. (1955): *Ibid.*, **9**, 62.
——, and Williams, D. C. (1956): *Biochem. J.* **64**, 578.
Cooling, C. I. (1958): *Ibid.*, p. 171.
Dukes, C. E. (1955): 'Classification of Tumours of the Bladder', Broad Sheet No. 1, Institute of Urology, London.
——, and Masina, F. (1949): *Brit. J. Urol.*, **21**, 273.
Marhsall, V. F., and Whitmore, W. F., Jr. (1956): *Cancer N.Y.*, **9**, 609.
Riches, E. W. (1955): *Ann. Roy. Coll. Surg. Engl.*, **18**, 178.
—— (1958): Lettsomian Lecture, *Trans. med. Soc. Lond.*, **74**, 77.
Wallace, D. M. (1956): *Ann. Roy. Coll. Surg. Engl.*, **18**, 366.
—— (1958): 'Tumours of the Bladder', Edinburgh.
Willis, R. A. (1953): 'Pathology of Tumours', 2nd ed., London.

CARCINOMA OF THE SKIN

By HUGH GORDON, *M.C.*, M.B., F.R.C.P.

Dermatologist, Royal Marsden Hospital; Physician in Charge, Skin Department, St. George's Hospital

THE conditions which have to be dealt with are the common cancers, basal-cell carcinoma (rodent ulcer) and squamous-cell carcinoma (epithelioma), and the pre-cancerous condition. A comparative newcomer is the so-called molluscum sebaceum which is not a cancer although up to comparatively recently it has been regularly diagnosed clinically and pathologically as an epithelioma. Finally there is melanoma, the black cancer in all senses.

RODENT ULCER AND EPITHELIOMA

As is well known rodent ulcer is usually only locally malignant and usually easily diagnosable both clinically and pathologically. Epithelioma does metastasize, though often very tardily. It must be pointed out, however, that baso-squamous tumours are not so uncommon, and therefore rodent ulcer should not be too lightly regarded both on account of this possible malignant change and also on its own account. It has an inveterate tendency to recur and if 'nibbled' at can become resistant to all treatment.

Rodent ulcer.—The clinical diagnosis of an established lesion of 1 centimetre upwards seldom presents any difficulty. About 70 per cent. occur in the quadrilateral bounded by a line drawn from the helix to the outer canthus above the lobe of the ear and the external commissure of the mouth below, 28 per cent. above and below down to the collar bone, and 2 per cent. scattered over the body often presenting difficulty in diagnosis. The preference for exposed sites indicates the two major predisposing factors: namely, trauma and above all sunlight, particularly in fair-skinned and blue-eyed types. The age incidence of 45 onwards is in keeping with cancer generally, although rodent ulcers occurring in the 20 to 30 age-group are by no means uncommon, usually in fair-skinned individuals.

The classical history is the presence on these sites of a chronic lesion which has persisted for years, growing slowly with periods of inactivity. The appearance of a small scab which gets knocked off and re-forms and occasional bleeding are important diagnostic points. As it develops, a hard-rolled edge becomes apparent, often with telangiectases running over it. Ulceration develops centrally and in certain angular sites, such as the orbit, nasal grooves and round the ear, can penetrate deeply with comparatively little showing on the surface. Commonly recognized clinical variants are the button type (fig. 1), cystic type, superficial scarring lesions (fig. 2), and those almost entirely composed of granulomatous tissue. The picture can therefore vary widely, but a hard cartilaginous edge which can often be more clearly felt than seen is a regular feature and is always present to some extent.

One clinical variety which is less well known is the multiple superficial type. This occurs mainly on the body but the face can also be included. The lesions have a flat scaly surface with minute areas of erosion which often heal. The raised edge is only just visible with a lens but this gives the lesion a clear-cut appearance—often as though it has been painted on the skin. The majority of cases give a history of having taken arsenic for a considerable period of years. They are often epileptics or have psoriasis.

FIG. 1.—Rodent ulcer—button type.

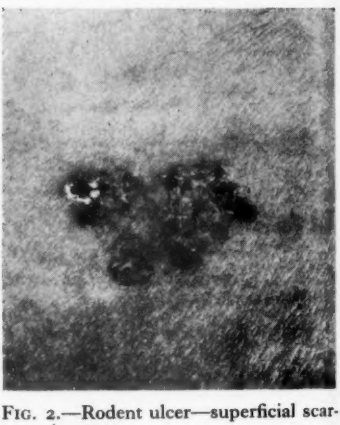


FIG. 2.—Rodent ulcer—superficial scarring type.

Epithelioma.—It is often impossible to distinguish the two clinically. Epithelioma exhibits a tendency to keratinization and later a ragged ulceration (fig. 3) without the scarring and healing often found in rodent ulcer. The edge of the tumour tends to be hard and fleshy without the cartilaginous consistency of the rolled edge of rodent ulcer. Surrounding inflammatory action is more commonly found in epithelioma. The history is often of help, being a question of months instead of years. Only epithelioma occurs on the mucous membrane and mucocutaneous junctions. Lesions on the ears are more commonly epithelioma than rodent ulcer. The back of the hand is a favourite site for epithelioma.

Differential diagnosis.—The differential diagnosis of any doubtful lesion must be settled by biopsy which necessitates a local anæsthetic. The question obviously arises therefore as to why the entire lesion should not be cut out at the same time. Indeed, if it is a very small lesion this is a very practical consideration. If it is adopted it is important that the excision be made on the definite assumption that the lesion is a rodent ulcer. That is to say, with a wide margin and adequate depth. On many areas, such as the neck and sides of the cheek where there is ample loose skin, this can be satisfactorily performed and yield a good cosmetic result. There are, however, many areas, particularly round the nose and eyes, where an adequate excision raises the question of a possible skin graft. Before proceeding to

this perfectly safe but necessarily more complicated procedure it is probably fairer to the patient to establish the diagnosis without any doubt.

Dermatologists often see very small lesions where the differential diagnosis cannot be established clinically with any certainty. A perfectly practical procedure in these cases is the insertion of a local anæsthetic and scraping out the lesion carefully with a sharp small spoon, taking care to get adequate depth and to keep the small piece intact. If necessary the bleeding surface can be lightly touched with a cautery to effect hæmostasis. This procedure is simple and does not worsen the scar if x-rays are subsequently found to be necessary.

FIG. 3.—Epithelioma which started four months previously, showing irregular outline.

All lesions on the face which are chronic and may gradually increase in size are candidates for differential diagnosis. In order of frequency these are the senile wart or solar keratosis, the common mole, sebaceous cysts, lupus erythematosus, lupus vulgaris and tertiary syphilide. The senile wart is a pre-malignant condition which most commonly becomes an epithelioma but may occasionally develop into a rodent ulcer.

The normal mole often enlarges in size but it retains normal hair follicles and a smooth consistent surface. Rodent ulcers, however, do occur in and around moles and after treatment by radiotherapy the mole remains intact. Difficulty may occur when this arises in a pigmented mole, owing to the fear of a melanoma. It must also be remembered that rodent ulcers sometimes contain pigment even when not arising from a pigmented mole. The other three conditions are all relatively uncommon and are in fact readily distinguishable clinically and with certainty by biopsy.

TREATMENT OF RODENT ULCER AND EPITHELIOMA

The twin pillars of treatment are radiotherapy and surgery, alternatively, or sometimes in combination. Statements or articles which have sometimes appeared expressing the overriding advantages of one method of treatment as opposed to the other are today unrealistic. Ideally the approach should be a joint one. The method of treatment depends upon the site of the lesion and its size. In rodent ulcers there is seldom any urgency and therefore the question of the patient's convenience and possibly purse should be considered. What is important is that whichever method of treatment is adopted it must be deployed fully and completely. The surgery must be competent

and thorough and the x-rays delivered equally competently by someone with an adequate experience and range of apparatus.

Surgery, even if a graft is necessary, has the advantage of being quicker. In the case of a simple excision there is only one small operation and the

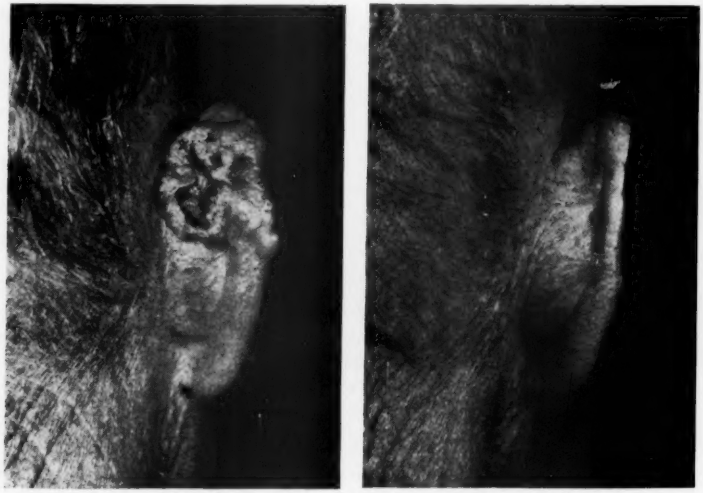


FIG. 4.—Epithelioma of the ear: before and after radiotherapy.

removal of stitches four to six days later. With a graft, admission to hospital is usually necessary and the time extended to ten days or a fortnight. With radiotherapy the actual treatment will consist of four to ten daily visits. There is probably little doubt that the application of a single dose gives worse results than split dosage. There is then the necessary reaction which starts about a week after termination of treatment and is seldom over completely before the end of a month. This can usually be fairly satisfactorily camouflaged but on prominent sites such as the tip of the nose may interfere with social activities. In practice, these general considerations apply fairly equally to both rodent ulcer and epithelioma, although in the latter cosmetic considerations are less important and urgency more so.

Some sites have special indications for radiotherapy, such as the lip, ear, round the orbit, and generally round the nose. Cosmetic results round the lip are excellent compared with surgery and this also applies to the ear. Even if the cartilage of the ear is involved, surprisingly good results can often be obtained by radiotherapy (fig. 4), cure sometimes resulting even with a permanent perforation of the ear. If the bone is involved surgery is absolutely essential.

Treatment of recurrent lesions.—It is in these that the real problems of treatment arise. Perhaps the most difficult is the case which has been treated by radiotherapy and presents within months or years with a small ulceration

in the treated area. This may be a radio-necrosis or a recurrence. The diagnosis may have to be established by a further biopsy. Radio-necrosis, of course, is undesirable, can give rise to a great deal of pain and is one of the disadvantages of radiotherapy as compared with surgery. It may, however, sometimes be taken as a calculated risk when there is a poor tumour tissue base and surgery is refused or for other reasons undesirable. In many cases, however, this superficial ulceration is transient and follows over-exposure to sunlight of the irradiated area. Healing is quickly established by the application of a hydrocortisone and neomycin ointment. This type of breakdown is more likely to occur in the centre of the treated area and a true recurrence at the edge. If the lesion is a true recurrence it must then be treated by surgery.

FIG. 5.—Molluscum sebaceum which started two months previously, showing smooth symmetrical outline.

In recurrence following surgery radiotherapy should be employed unless the recurrence is a deep one involving bone when more elaborate surgical removal is required.

MOLLUSCUM SEBACEUM

This lesion is now fully established as an entity. Its appearance conforms to the textbook description of epithelioma; in fact, some photographs in textbooks, particularly those illustrating tar cancer, look suspiciously like examples of molluscum sebaceum. Its characteristic is very quick growth. It starts as a small hard papule which may stay stationary for some weeks. Then, suddenly, after possibly trauma or for no obvious reason, rapid growth occurs, and a lesion with a diameter of 1 centimetre is attained in three to four weeks. It has a fleshy base, a firmly embedded keratotic plug, often a red areola, and sometimes a whitish look. It gives the appearance of sitting on top of the skin (fig. 5).

Up till 1950 biopsy specimens were regularly reported as actively growing epitheliomas. Rook and Whimster then presented a paper calling attention to the condition and giving it the name of molluscum sebaceum under which it was in fact first described by MacCormac and Scarff in 1936 and apparently then forgotten. They mentioned the fact that, if left, this lesion involuted on its own. This was soon confirmed by other observers (e.g. Gordon and Musso, 1950). Many articles have appeared since, the most recent being by Sidney Thompson, in 1958, which collects thoroughly

combined British dermatological experience. It is now agreed that the pathological picture is a tolerably clear one if the whole or at least half the lesion is removed for section.

The lesion usually occurs on the exposed areas, most commonly the face, and is usually single. The age incidence is indefinite, although Thompson's figures indicate that it is twice as common in those aged fifty and over than in the younger age-groups. The etiology is unknown. The ordinary tar wart (fig. 6) can develop into a lesion clinically and pathologically identical with molluscum sebaceum; on the other hand, it may develop into an epithelioma.

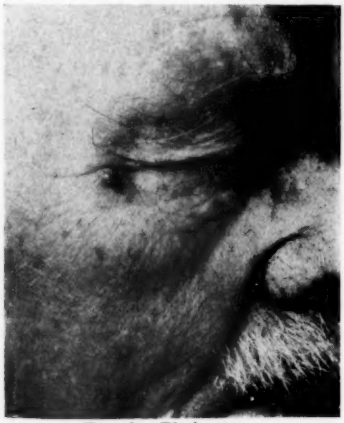


FIG. 6.—Pitch wart.

Treatment.—If the diagnosis is certain and the condition is self-resolving, theoretically no treatment is necessary. Such resolution, however, may take three or four months and is unsightly in the process. The crust falls out leaving a ragged granulating surface which is slowly absorbed. The resulting scar is usually slight and often depressed. Apart from cosmetic considerations, one is inevitably unhappy at leaving a potentially malignant lesion without definite diagnosis.

Tar lesions on the hands and scrotum and probably suspected molluscum sebaceum on the hands of non-tar workers should be treated as potential epithelioma. Biopsy is essential and for reasons already given complete removal desirable, this, however, can be quite a narrow excision.

Many dermatologists favour planing the lesion flat with the surface and then lightly cauterizing the base. Whilst this gives a good cosmetic result the resulting lack of depth in the biopsy specimen may give the pathologist some difficulty. Further, unless the cauterization is very thorough, fresh growth may recur. My own practise is to cut round the base to the depth of half a Bard Parker no. 15 blade held at a slightly inverted angle. The bleeding is stopped with the cautery. This gives adequate depth for the biopsy and the resulting scar is excellent.

MALIGNANT MELANOMA

This practically always arises at the site of a pigmented lesion. Differences of opinion exist as to the proportion in which its antecedent lesion is a pigmented nævus. Becker (1954) holds that 75 per cent. of malignant melanomas arise from what he terms lentigo maligna, a brown flat macule rising *de novo* after puberty which gradually increases in size and depth of pigment but contains no true nævus cells. Cunningham (1952) in a series of approxi-

mately twelve hundred cases collected from the literature estimates that pigmented nævi are the forerunners in 56 per cent.

The type of pigmented nævus which is generally accepted on pathological grounds to be potentially malignant is the junction nævus. This arises before puberty often in showers of flat, hairless, brownish to black macules. This is the only type which occurs on the palms, soles, genitalia, and mucous membranes. Malignant change is very rare indeed before puberty. Occasionally when removed before puberty these lesions have histological features indistinguishable from malignant melanoma, but they are in fact benign. The common mole occurring anywhere on the body but most commonly on the face is usually the intradermal type. This is often hairy, tends to be raised and fleshy, and often increases in size. Pigment varies but is seldom deep. Malignant change does not occur. Unfortunately compound nævi occur, clinically resembling the intradermal type but with some junctional activity present. The so-called 'blue nævus', a rare intradermal lesion, very seldom becomes malignant.

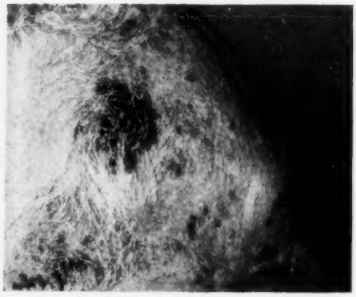


FIG. 7.—Seborrhœic wart.

The characteristic features of a malignant melanoma are:

(1) Increase in pigmentation in a pre-existing mole or pigmented macule. This increase is variable and not uniform, showing instability.
(2) Radial extension, or a peripheral halo, of pigmentation.
(3) Increase in size of a mole either above the surface or radially.
(4) Ulceration or scabbing.
(5) Metastatic pigmented lesions.
(6) Hæmorrhage or serous exudation from the lesion.

It must be remembered that ordinary moles, particularly if hairs are pulled out, may get inflamed and even discharge. This is not necessarily significant.

Differential diagnosis.—This is by no means easy as is evidenced by two recent American series (Becker, 1954; McMullan and Hubener, 1956). The clinical diagnosis was only confirmed pathologically in 43 per cent.; conversely, in cases diagnosed pathologically the clinical diagnosis was only confirmed in 48 per cent. In both series the lesion most commonly confused with malignant melanoma was the innocent pigmented nævus. After that came the seborrhœic wart (fig. 7). This is usually multiple but can look very black as it may contain melanin. If the lesion is single, irritated and secondarily infected, differential diagnosis may be very difficult. The other two conditions which entered into the differential diagnosis were pyogenic granuloma and pigmented basal-cell carcinoma.

Antecedent trauma, whether frictional, surgical (insufficient excision), or dermatological (cautery or diathermy), is often quoted as a predisposing

factor. Cade (1957) judiciously points out that this is only presumptive, an alternative explanation being that the malignant melanoma was already highly malignant and inadequate treatment failed to control it.

A patient, aged 45, presented with a small warty lesion on his back with a doubtful history of duration—probably a few years. He had recently knocked it and it had bled. It presented as a small pedunculated fleshy lesion with a black area at the base. This was thought to be hæmosiderin but it was felt justifiable to remove the lesion by planing and it was sent for biopsy, largely to determine the nature of the pigment. The section confirmed this to be melanin and doubt was expressed as to its possible malignancy. Within ten days therefore the site of the lesion was widely excised and a further biopsy revealed nothing except slight scar tissue. Within three months, however, the patient developed a granulomatous lesion of the tonsil, enlarged glands in the neck, and three nodules over the chest. These were all confirmed to be malignant melanomas.

FIG. 8.—Xeroderma pigmentosa, with epithelioma of left upper lip.

It could be said that the original procedure had caused or contributed to the explosive sequelæ. The second biopsy, however, speaks strongly against this and it seems more probable that the original lesion was in fact highly malignant and that metastases had already occurred.

Fleshy, hairy moles are probably quite safely treated by methods other than surgical. A recent questionnaire to American dermatologists revealed that 70 per cent. used non-surgical methods in over 90 per cent. of cases (Shaw, 1953). Becker (1949) planes the lesion level with the skin and sends it for biopsy to exclude any junctional activity. Flat pigmented nævi should be excised if their removal is desired. Whilst extensive prophylactic removal of deeply pigmented nævi is probably undesirable, it is common to consider it on marked frictional areas.

There is a widespread fear of touching a suspicious lesion other than by surgical removal. If the lesion is small total removal is obviously better than biopsy. If, however, it is large, such removal may lead to unnecessary mutilation, or alternatively an expectant policy which may be dangerous. Shaw (1953) and others feel that it is a safe procedure always assuming that further radical surgery is available within a week.

Treatment.—Once the diagnosis is established the treatment is entirely surgical. The primary lesion is radio-resistant though very occasionally glands and metastases do respond. Excision must be wide with at least 2 cm. margin and possibly up to 5 cm. in large lesions; and it must include deep fascia. A graft is necessary.

If glands are palpable and operable block dissection is essential, Cade recommends that this be done in continuity of the primary lesion if possible. He does not consider the excision of a connecting strip from the primary to distant glands a useful procedure. If the glands are not palpable some difference of opinion exists as to whether or not to adopt an expectant attitude. Raven (1950) states that 50 per cent. of cases show malignant melanoma cells in non-palpable glands and advises prophylactic removal within a fortnight.

PRE-CANCEROUS CONDITIONS

Those of importance have already been mentioned: namely, senile keratosis, pitch wart and lentigo maligna. The others usually considered are Bowen's disease, Paget's disease of the nipple, and erythroplasia of the penis and possibly xeroderma pigmentosa. These are all rare conditions with the exception of Paget's disease of the nipple which is associated with a deep duct carcinoma. Bowen's disease presents as a single plaque usually on the body, and increasing very slowly in size. Pathologically the picture is the same as in Paget's disease, namely, an intra-epidermal epithelioma. There is, however, no associated deep carcinoma, but a final breakdown into an ordinary squamous epithelioma is to be expected after five to fifteen years. The same holds for erythroplasia.

Xeroderma pigmentosa (fig. 8) manifests itself early in life by a complete inability to stand ordinary sunlight. The exposed areas are extensively freckled by the age of two or three. Epitheliomas develop round about the age of four or five and continue remorselessly. If, however, adequate steps can be taken to prepare an opaque light-resistant cover cream, epitheliomas can be prevented. One such case at the Royal Marsden Hospital had four lesions treated between the age of five and ten. She is now eighteen and has had no further lesion for eight years.

References

Becker, S. W. (1949): *Arch. Derm. Syph.* (*Chicago*), **60**, 44.
—— (1954): *Ibid.*, **69**, 11.
Cade, S. (1957): *Brit. med. J.*, **i**, 119.
Cunningham, J. A. (1952): 'Progress in Fundamental Medicine', p. 52.
Gordon, H., and Musso, L. (1950): *Proc. Roy. Soc. Med.*, **43**, 838.
MacCormac, H., and Scarff, R. W. (1936): *Brit. J. Derm.*, **48**, 626.
McMullan, F. H., and Hubener, L. F. (1956): *Arch. Derm. Syph.* (*Chicago*), **74**, 618.
Raven, R. W. (1950): *Ann. Roy. Coll. Surg. Engl.*, **6**, 28.
Rook, A. (1950): *Rapp. Ass. Derm. Syph.*, **9**, 221.
Shaw, C. (1953): *Sth med. J.* (*Bgham., Ala.*), **46**, 286.
Thompson, S. (1958): *Ann. Roy. Coll. Surg. Engl.*, **22**, 363.

THE PROBLEM OF FÆCAL INCONTINENCE IN GERIATRICS

By T. N. RUDD, M.D., M.R.C.P.

Consultant Physician, Geriatric Unit, Southampton Group of Hospitals

FÆCAL incontinence is one of the most distressing symptoms in geriatric practice: it is also the most easily controllable. The key to the situation lies in the fact that fæcal incontinence is hardly ever a condition 'in its own right', but the end-result of fæcal impaction. This lack of understanding is difficult to explain unless it is part of the scant attention which the whole matter receives even from geriatricians.

In his immensely long book, 'Geriatric Medicine', Stieglitz (1954) describes fæcal impaction, but nowhere refers to fæcal incontinence, which does not figure in his full index. Thewlis (1946), in 'The Care of the Aged', makes several useful references to impaction, but again no mention of fæcal incontinence. Even John Ryle (1948), writing on 'Ball valve accumulations in the rectum' in his 'Natural History of Disease', was apparently unaware of this important association.

Senile mental changes, of course, play a part in the origin of the condition. Old people often show diminished perception of rectal overloading and, even when they feel discomfort, are sometimes unable to communicate their needs. Intra-rectal pressure progressively increases as fæcal accumulation goes on and, as a result of bacterial action which ultimately liquefies the stool, the resistance of the stretched sphincter is finally overcome, and an incontinent bowel action results, followed by further incontinence until the anal ring regains its normal tone.

This is not to say that bowel incontinence of neurogenic origin does not exist. Major neurological disturbance can, of course, disturb rectal function. But the vast preponderance of rectal incontinence among geriatric patients is not 'cerebral' or neurogenic in origin. There are, of course, some cases of gross senile deterioration where there is a disorder of habit. Such cases are fairly easily recognized: the patient passes motions of normal frequency and consistency in inappropriate places, in his clothes or on the ward floor. He is generally unperturbed by his anti-social conduct and usually shows other signs of mental abnormality. That such cases exist should not allow us to overlook the quite different condition of incontinence arising from a missed fæcal impaction.

CAUSATION

Although the mechanism of fæcal impaction is generally well understood, the processes in its production may usefully be summarized. The two basic factors at work are constipation and a failure to empty the rectum completely. There is generally superadded a lack of awareness of rectal distension, due to central causes. Any of the usual causes of constipation may be at

work: special mention should be made of dehydration (from diminished fluid intake and such as follows a severe melæna), the use of high-residue food substances, such as bran preparations, or 'bulk' laxatives such as methylcellulose, the administration of barium salts in diagnostic radiography and the use of analgesics, such as codeine, which slow peristalsis. Poor muscle tone and strength fail to effect clearance, whilst an inadequate partial evacuation may deceive the patient that bowel action is normal, and thus obscure the clinical history.

The bowel contents, so retained, harden through the absorption of fluid. The resulting mass is moulded by bowel movement and lubricated by the excretion of mucus which its presence promotes. The mass remains *in situ*, acting at times as a ball-valve, until it ultimately breaks down, as a result of bacterial action. Meanwhile, soft fæces accumulate above it, and these may be discharged intermittently through a distended and weakened anal ring. This stretching of the sphincter is directly due to the downward pressure of the fæcal mass. At this stage, inspection of the perineum will show a bulging anus, through which at times the ball-valve mass may be seen. Pressing-down movements actually produce crowning and perhaps delivery of the mass, in a fashion similar to the birth of a fœtal head.

When liquid fæces are discharged, distinction between a primary impaction and true diarrhœa can easily be made. The liquid motions of fæcal impaction are thick and high-coloured, and not fully absorbed by the clothes, as would occur with a true diarrhœa from excessive peristalsis. When the fæcal mass disintegrates, a soft semi-solid motion results, adhering to the skin and perineal hairs. Such a sight clearly indicates the diagnosis, which can be confirmed by rectal examination.

Before natural cure is achieved by disintegration of the rectal mass, the patient is in danger of acute intestinal obstruction, which may be fatal whether or not an operation is carried out. Although in young subjects severe local pain may be experienced while expulsive movements are being attempted, pain in the very old is quite unusual. Accumulation of fæces in the colon above may lead to much abdominal distension, the overloaded bowel being easily palpable at times. The progress of the condition can best be observed throughout its course by digital examination, the only difficulty occurring in the unusual case of an impaction high in the rectum, beyond the reach of a finger.

DIAGNOSIS

The diagnosis of fæcal impaction is easy if its various manifestations are remembered and if it is accepted that the only sure method of detection is digital examination of the rectum. That fæcal incontinence should be considered as due to fæcal impaction until full examination has excluded the latter, should be considered as a medical aphorism. The fallaciousness of diagnosing the presence or absence of the condition on the result of enema

administration needs emphasis. In the presence of a ball-valve accumulation or a hard mass of dried fæces, an enema may either produce no result, or else an unsatisfactory one, either condition perhaps leading to the false idea of an empty bowel. When there is no incontinence, a distended rectum may be suggested by restlessness or by retention of urine: either of these two symptoms warrants a rectal examination. Indeed, so common is silent fæcal accumulation in the elderly that geriatric patients should have a routine rectal examination when first taken under care.

TREATMENT

The first therapeutic action is to empty the bowel. Unless the fæces are stony hard and wedged in position, a simple enema should be given, repeating this if an encouraging result is obtained. Throughout the clearance, by whatever method, progress must be observed by repeated digital examination. Two useful and time-saving alternatives to soap and water enemas may be considered. The first is to give a calcium chloride enema (4 fluid ounces [115 ml.] of a 5 per cent. solution) by the technique described by Howell (1956). The fluid is run rapidly into the upper part of the rectum, and a good result is often obtained, more quickly than with the bulkier soap and water enema, and with a lower incidence of shock in frail patients. When much soft matter is present, good evacuation is often obtained by the insertion of a 'dulcolax' suppository high in the rectum, instructing the patient not to attempt defæcation for at least twenty minutes. If no result is obtained, a further suppository can be used in two hours.

Softening of the fæces may be achieved by a retention enema of four fluid ounces (115 ml.) of olive oil or by adding three fluid ounces (85 ml.) of glycerin to a simple enema solution. In spite of every effort, digital fragmentation of the mass, followed by manual removal, is often needed. This is generally very painful and may need a general anæsthetic. Before this extreme measure is taken, disimpaction following a non-constipating analgesic should be tried: for this, 12 ml. of methylpentynol may be found useful. Two to three weeks' treatment may be required to empty a grossly overloaded bowel.

Subsequent management lies in preventing constipation and further impactions by instituting a regime designed to avoid such happenings. Comfortable, unhurried defæcation on a water closet, a commode or sanichair, and the absolute avoidance of bed-pans are essential. Fluid intake and diet should be adjusted to ensure adequate fluid and protein. Periodic rectal examination should be made if elimination is in doubt. A weekly enema is sometimes necessary, although there are grave objections associated with enema-neurosis and the strain on the busy nurse. Equally satisfactory results are generally obtainable by giving two 'dulcolax' tablets at night, once weekly, a 'dulcolax' suppository being used rectally next morning. As shown by Clark (1957), such a technique can greatly reduce or abolish the

need for enema administration. It needs to be stressed that 'dulcolax' contains an active 'contact' laxative, and cannot satisfactorily be replaced by the less-expensive glycerin pessary.

A final word of warning must be given. After any incident of fæcal impaction, the anal ring is distended and temporarily inefficient: true incontinence may occur until normal tone returns in a few days' time. Unless this is understood, the nurse and doctor may conclude that their efforts have been wasted, and the patient is unjustifiably labelled 'incorrigibly dirty'.

SUMMARY

Happiness in old age is dependent upon both physical and mental factors. Mental confusion and incontinence of bladder or bowel are responsible for much personal distress, and warrant every effort possible by practitioners and nurses to relieve them. The frequency and persistence of fæcal incontinence are largely due to a failure of attendants to realize that the condition originates, not in mental failure or deterioration of habit, but in the natural breakdown of retained fæces, resulting from a condition of missed constipation.

The onus of remedying the distressing incontinence thus lies on the practitioner and nurse to prevent the underlying constipation and to relieve the fæcal accumulation before natural breakdown results. To blame the patient for something which is under our control (but not within his), is only to add insult to injury and to facilitate his onward progress into senile dementia, which we all should wish to prevent.

References

Clark, A. N. C. (1957): *Brit. med. J.*, **ii,** 866.
Howell, T. H. (1956): *Nursing Mirror,* **103,** viii.
Ryle, J. A. (1948): 'The Natural History of Disease', 2nd ed., London.
Stieglitz, E. J. (1954): 'Geriatric Medicine', 3rd ed., Philadelphia and London.
Thewlis, M. W. (1946): 'The Care of the Aged', 5th ed., London.

THE TREATMENT OF ACUTE BARBITURATE POISONING

By S. G. FLAVELL MATTS, M.B., M.R.C.P.Ed.
Medical Registrar, Southmead General Hospital, Bristol

Since the first death from barbiturate poisoning was reported in 1903, by Gerhartz, an increasing amount of attention has been focused on the treatment of this condition. Many advances have been made, and regimes of therapy have been suggested by Nilssen (1951) and Koppanyi and Fazekas (1950, 1952, 1954). Recently, β-ethyl-β-methylglutarimide (bemegride) has been more widely used, following its introduction by Shaw *et al.* (1954). The purpose of my investigation was to assess the value of bemegride in routine clinical use, and to attempt to simplify the indications for its employment.

SELECTION AND CLASSIFICATION

The series consisted of 80 cases of barbiturate poisoning which were admitted as emergencies (table I). They were completely unselected and may be taken to be representative of the type of case seen in ordinary clinical practice. They were all examined personally on admission and a system of grading was devised to indicate their severity:—

Grade I.—Drowsy, semicomatose or even sufficiently sleepy to be called comatose, but must be capable of responding to stimuli (painful or otherwise). All reflexes present including corneal, pharyngeal and laryngeal. No evidence of respiratory depression.

Grade II.—Comatose and unresponsive to ordinary stimuli. Tendon reflexes depressed, corneal reflex + or o, pharyngeal reflex + or o, laryngeal reflex present and pupils reacting to light. Respiration probably depressed but not below 8 per minute. Blood pressure recordable.

Grade III.—Deeply comatose. All tendon reflexes depressed or absent. Corneal, pharyngeal and laryngeal reflexes absent. Pupils non-reactive to light. Respiration markedly depressed even down to 3 to 4 per minute. Signs of marked peripheral circulatory failure and shock present with a low or unrecordable blood pressure.

This general classification worked quite well but was improved by the use of sub-groups IA and IIA in cases showing some features of groups I and II, and II and III respectively. It was found that this method helped greatly in determining the method of treatment, in particular whether or not to use bemegride.

THERAPY

Grades I and IA.—These patients received no specific therapy but were observed closely.

Grade II.—Some of these received bemegride by intermittent intravenous injection, the regime being 50 mg. per dose, and the total dosage being whatever was required to lighten their state of consciousness.

Grades IIA and III.—All these were treated with intravenous bemegride, 50 mg. doses into the drip at five-minute intervals, until the patient reached

the 'safe' state. This consists of a return of muscle tone and reflexes, including pharyngeal, laryngeal and corneal. It is usually associated with a return towards normal blood pressure, pulse rate and respiratory rate and may be associated with groaning and voluntary movements.

In all, 31 patients received bemegride.

The comatose patient was under continual observation. All grade III patients had endotracheal intubation carried out on admission and the tube was left in position until the depth of coma was lightened with the return of laryngeal and pharyngeal reflexes. For those in whom response was slow or coma prolonged, tracheotomy was performed as it gives better control of respiration. A positive pump respirator was available but its use was not, in fact, necessary in any of the cases.

Grade I	28 cases
Grade 1A	4 cases
Grade II	24 cases
Grade IIA	4 cases
Grade III	20 cases
	80 cases

TABLE I.—Classification of 80 cases of barbiturate poisoning.

All patients were fed by gastric tube with the usual egg-milk-'casilan'-vitamin mixture two- to three-hourly. Those cases in which coma was prolonged beyond twenty-four hours received antibiotic cover to prevent chest and urinary complications. Physiotherapy was employed to the legs and chest. The patients were all turned hourly and the usual nursing care of the skin, mouth, eyes, bladder and bowel was employed.

Episodes of collapse with lowered blood pressure responded well to intravenous noradrenaline transfusion in a concentration of 16 mcg. per ml. in normal saline, combined with the administration of further dosage of bemegride, 50 mg., and amiphenazole, 15 mg., repeated as necessary. It was found possible to produce almost immediate response to these measures and for this reason all grade III patients had a transfusion set up on admission and kept running until they were out of danger. This enabled immediate intravenous therapy to be employed if necessary.

RESULTS

Bemegride did not shorten the period of unconsciousness significantly in the more severe cases but did lighten the depth of the coma considerably. In the milder cases, it brought the patient rapidly to consciousness. Most patients were brought to the 'safe state' in two to three hours and did not relapse. This resulted in a great saving of nurses' and doctors' time, as the patients did not require so much attention subsequently and the incidence of complications was considerably reduced.

The death rate was 1 in 80 cases (1.25 per cent.). If only the severely comatose patients are considered, it amounted to 1 in 24 cases (4 per cent.). This compares favourably with other series published. The significant necropsy findings in the patient who died were as follows:—

Marked œdema of the lungs and early broncho-pneumonia. Heart somewhat dilated with pale myocardium. Anterior coronary artery atheromatous and occluded about 1½ inches (3.8 cm.) from its origin; distal to this were the usual changes in the myocardium of a recent infarct. The brain was mildly œdematous and there

were a few punctate hæmorrhages in the mid-brain region. The arteries generally showed moderate degenerative changes.

DISCUSSION

Up to 1954 there was considerable disagreement about the treatment of barbiturate poisoning and opinions differed widely from one centre to another.

The assessment of the pharmacological properties of bemegride by Shaw *et al.* (1954), and its successful clinical use by Shulman *et al.* (1955), were hailed by most people as being the therapeutic answer to this problem. Certain authorities, however, who had specially equipped centres for the treatment of barbiturate poisoning, disagreed and disputed the value of bemegride, especially denying its so-called antagonistic effect on the barbiturates (Locket, 1956; Plum and Swanson, 1957; Nilssen, 1957); other workers, while acknowledging its value, also denied the antagonistic effect on barbiturates (von Planta and Klingler, 1956; Frey *et al.*, 1956; Hahn *et al.*, 1956; Böttiger *et al.*, 1957). The main exponents of the idea that bemegride is a specific barbiturate antagonist have based their work on its arousing effect in animals or in terminating barbiturate anæsthesia in humans (Shaw *et al.*, 1954; Shaw, 1955; Harris, 1955; Bentel *et al.*, 1956; Turner and Hodgetts, 1956; Wyke and Frayworth, 1957).

In considering these views, I feel strongly drawn towards the old adage that when two groups of opinions differ widely then the truth must lie somewhere between the extremes that they are advocating. If it were true that bemegride is a specific antagonist of barbiturates, one would expect that after a suitable amount had been administered the barbiturate would have been neutralized and the patient's recovery steady and uneventful. This certainly applies in a large number of cases but, in my own experience and in all the larger published series, there are cases which have relapsed and required further therapy with bemegride after the 'safe state' had been reached. That this is due to further absorption of barbiturates from the alimentary tract is most unlikely as, in some cases, periods of up to seven days had elapsed before this occurred and surely, by then, all the available barbiturate must have been absorbed. The second viewpoint, that favours a purely analeptic action, cannot explain the undoubted arousing effect of bemegride and its ability to reverse the effect of barbiturates used in anæsthesia. Neither of these actions can be exactly duplicated by any of the other analeptics that have been used in clinical or experimental studies although the difficulty in interpreting results of this kind has been stressed recently by Thomson (1958). I would suggest that the value of bemegride rests partly on an analeptic effect, and partly on a functional barbiturate antagonism which varies from patient to patient in its intensity.

The next question to be considered is the value of bemegride in barbiturate poisoning. This is extremely difficult to assess. A consideration of mortality rates tends at first to give a false impression. Most of the figures are based on large series published by special centres for the treatment of barbiturate poisoning; these suffer from the disadvantage of being representative not of the general mortality rate to be expected but that which can be obtained with a specially equipped unit working under the best of conditions.

The following is a selection of recent figures from various centres *not* employing bemegride:—

Nilssen (1951) reports an over-all mortality rate of 1.7 per cent. For cases of moderate or greater severity he gives a figure of 3.4 per cent. Hahn and Rossle (1956) give an over-all death rate of 5.5 per cent. for moderate to severe cases. Locket (1956) quotes a mortality rate of 1.8 per cent. for his series of 1000 cases, 326 of which were moderate to severe. This gives a figure of 5.5 per cent. for the more severe cases. Plum and Swanson (1957) give an over-all figure of 1.7 per cent. mortality rate but, if only the more severe cases are considered, this rises to 6 per cent.

Thus, if we take only the more severe type of case treated in a special centre, we get mortality rates of 3.4 per cent., 5.5 per cent., 5.5 per cent. and 6 per cent. This may be compared with the figure of 20 per cent. reported by Riishede (1950) for severe cases not treated in a special centre.

An analysis of the reported cases, mostly of moderate to great severity, treated with bemegride shows a mortality rate of 3.2 per cent. and my own series (only considering severe cases) 4 per cent. Although this is not greatly below that obtained without bemegride, its significance is magnified by the fact that these cases are taken from all over the world and not, in the most part, from specialized units. Thus it seems reasonable to conclude that bemegride has shown itself to be of general value in routine clinical use without the necessity for special equipment and a trained team.

Other points that have been put forward in its favour are that by lightening the depth of coma it shortens the period during which the patient requires very close observation by medical and nursing staff and thus eases the burden of therapy in a busy general hospital. This is of doubtful validity as the possibility of relapse, although unlikely, means that vigilance cannot be relaxed too soon and there is no convincing evidence that bemegride shortens the period of coma in the severe cases, although definitely lightening it, and thus improving the chances of ultimate recovery.

There seems to be little doubt that bemegride is best given into an intravenous transfusion, and my own experience suggests that the intermittent method gives the best control and, as it should only be given by a doctor, ensures constant medical attention during its employment. The dosage required cannot be accurately predicted in advance. This is probably due to the variation in individual tolerance to barbiturates; it is obvious after examining the reported cases that the amount of barbiturate the patient has taken does not bear a direct relationship to the depth of coma induced. It is quite common to find a large dose inducing only a light coma whilst a comparatively small dose may result in severe coma in certain individuals. Similarly, some severe cases of barbiturate poisoning require only small doses of bemegride and others large doses. This may be due to individual variation in sensitivity. Amiphenazole (2:4-diamino-5-phenylthiazole) has proved to be of little value in treatment. My own experience is in accordance with that of other workers (e.g. Frey *et al.*, 1956; von Planta and Klingler, 1956) that patients treated with bemegride alone do equally well. It is possible, however, that cases with extreme respiratory depression may benefit

from the combination and it is recommended for this type of case only.

With regard to side-effects of bemegride, convulsions can be induced by overdosage but these are easily controlled with small doses of thiopentone (0.1 to 0.2 g.). Psychoses have been reported by Kjaer-Larsen (1956), but this finding has not been confirmed from any other source, and I have found no evidence of this in my own series of cases.

I feel that bemegride is unnecessary in cases of mild or moderate severity (grades I and II) as these patients will recover spontaneously and no deaths have been reported in this type of case. It should certainly be employed in all more severe cases (grades IIA and III) and the earlier therapy is started the better. It is not suggested that bemegride can replace other general measures, such as those to aid respiration, maintain blood pressure, and prevent infection, but should be employed in addition to these.

SUMMARY AND CONCLUSIONS

An assessment of the value of bemegride ('megimide') in the treatment of barbiturate poisoning is made by reference to published reports, consideration of mortality rates, and presentation of a series of cases treated with it.

A system of grading for cases of barbiturate poisoning is suggested and ways in which this would help in deciding upon the use of bemegride are discussed.

The mode of action and method of employment are considered.

It is concluded that bemegride is of value in the more severe cases of barbiturate poisoning and that its mode of action is partly by functional barbiturate antagonism and partly by an analeptic effect.

I would like to express my thanks to Dr. J. M. Naish, Dr. C. J. Fuller, Dr. C. Seward and Dr. A. J. Daly for permission to publish details of cases.

References

Bentel, H., Barlow, M. B., and Ginsberg, H. (1956): *Med. Proc.*, **2**, 198.
Böttiger, L. E., Engstedt, L., and Strandberg, O. (1957): *Lancet*, **i**, 932.
Frey, H. H., *et al.* (1956): *Arzneimittel-Forsch.*, **10**, 583.
Gerhartz, (1903): *Berl. klin. Wschr.*, **40**, 928.
Hahn, F., Oberdorf, A., and Schunk, R. (1956): *Dtsch med. Wschr.*, **81**, 1580.
——, and Rossle, I. (1956): *Med. Mschr.*, **10**, 367.
Harris, T. A. B. (1955): *Lancet*, **i**, 181.
Kjaer-Larsen, K. (1956): *Ibid.*, **ii**, 967.
Koppanyi, T., and Fazekas, J. F. (1950): *Amer. J. med. Sci.*, **220**, 559.
——, —— (1952): *Ibid.*, **224**, 577.
——, —— (1954): *Curr. Res. Anesth.*, **33**/1, 58.
Locket, S. (1956): *Proc. Roy. Soc. Med.*, **49**, 585.
Nilssen, E. (1951): *Acta med. scand.*, **139**, Suppl. 253.
—— (1957): *Brit. med. J.*, **ii**, 290.
Plum, F., and Swanson, A. G. (1957): *J. Amer. med. Ass.*, **163**, 827.
Riishede, J. (1950): *Ugeskr. Læg.*, **112**, 507.
Shaw, F. H., (1955): *Med. J. Aust.*, **ii**, 889.
—— *et al.* (1954): *Nature (Lond.)*, **174**, 402.
Shulman, A., *et al.* (1955): *Brit. med. J.*, **i**, 1238.
Thomson, T. J. (1958): *Ibid.*, **i**, 976.
Turner, A. W., and Hodgetts, V. E. (1956): *Aust. vet. J.*, **32**, 49.
von Planta, P., and Klingler, M. (1956): *Schweiz. med. Wschr.*, **86**, 691.
Wyke, B. D., and Frayworth, E. (1957): *Lancet*, **ii**, 1025.

HEXETIDINE IN VAGINAL REPAIR OPERATIONS

By J. M. HOLMES, M.D., M.R.C.O.G.

Resident Obstetrician and Obstetric Tutor, Queen Charlotte's Maternity Hospital, London

POSTOPERATIVE wound infection following pelvic floor repair operations remains a constant hazard in spite of a high standard of sterilization and surgical technique (Lunt *et al.*, 1957) and the liberal use of antibiotics. Many of these operations are performed after the menopause or in the presence of chronic cervicitis. The protective influence of the Döderlein's bacillus has gone, the vaginal fluid has become alkaline and potentially pathogenic organisms are able to thrive. A mild cellulitis associated with pyrexia, poor healing, formation of granulation tissue and a profuse offensive discharge, which may persist for several weeks after operation, have been accepted as a common trend of postoperative events. Occasionally more serious complications, such as deep vein thrombosis and embolism, secondary hæmorrhage and septicæmia, may follow and these are mainly responsible for an operative mortality of nearly 2 per cent.

Efficient sterilization of instruments and gauze swabs (Bowie, 1955), controlled positive-pressure ventilation of theatres with filtered air, a strict adherence of theatre staff to aseptic principles, the exclusion of carriers and the isolation of septic cases will do much to reduce the incidence of infection. Nevertheless, the vagina often harbours pathogenic organisms and when the protective barrier of the vaginal epithelium has been broken infection can become established. To diminish this risk preoperative douching and the application of various antiseptics and antibiotics have been recommended with some success (Browne, 1955; Champ, 1955; Marbach, 1948).

HEXETIDINE

Hexetidine ('sterisil') is 5-amino-1:3-di-(2-ethylhexyl)hexahydro-5-methylpyrimidine and is prepared as a vaginal gel in a concentration of 0.1 per cent. at a pH of 4.2. It exerts a bactericidal action by interfering with vital metabolic processes necessary for bacterial growth, and this includes thiamine antagonism (Edwards *et al.*, 1956). It has great affinity for tissue without loss of antimicrobial activity and its removal by physiological and pathological secretions is achieved only with great difficulty. *In vitro* studies have revealed a wide range of micro-organism sensitivity. Most staphylococci and streptococci are sensitive in the range of 1 to 15 micrograms per ml., whilst coliform organisms and Pseudomonas strains are generally inhibited by concentrations of 100 to 150 micrograms per ml. Many pathogenic fungi including *Candida albicans* are also sensitive. Cross-resistance

with penicillin and other antibiotics does not develop. Topical application of hexetidine, 0.1 per cent., in 600 patients with infections of the vagina and skin has produced no signs of irritation, sensitization or systemic toxicity. It does not appear to interfere with the normal processes of healing.

CLINICAL TRIAL

Patients were admitted to hospital two days before operation, vaginal ring pessaries were removed, the vagina inspected and clinical vaginitis excluded.

Operation	No. of patients in hexetidine group	No. of infections in hexetidine group	No. of patients in control group	No. of infections in control group
Anterior and posterior colpoperineorrhaphy	10	1	12	5
Manchester repair	37	2	35	11
Cervical amputation	3	1	3	1
Total no. of patients	50	4	50	17

TABLE I.—Incidence of postoperative infection following vaginal repair operations.

A high vaginal swab was sent for culture. With the aid of a cardboard disposable applicator, 7 ml. of hexetidine gel were deposited in the upper part of the vagina and this constituted the only preoperative vaginal preparation. Immediately following the completion of the pelvic floor repair a

	Hexetidine group		Control group	
Preoperative culture of high vaginal swab	*E. coli*	25	*E. coli*	26
	B. proteus	8	*B. proteus*	10
	Staph. aureus	3	*Staph. aureus*	3
	No pathogens	14	No pathogens	11
Postoperative culture of vaginal infections	*E. coli*	1	*E. coli*	8
	B. proteus	2	*B. proteus*	7
	Staph. aureus	1	*Staph. aureus*	1
			Beta-hæmolytic streptococcus	1

TABLE II.—Pre- and post-operative findings in patients undergoing vaginal repair operations.

further application of hexetidine was made and the vagina firmly packed with a sterile gauze roll for twenty hours. The control group received two preoperative vaginal douches with 1 per cent. aqueous flavine, and a post-operative vaginal pack soaked in acriflavine paraffin emulsion was inserted for twenty hours. Open bladder drainage was maintained for forty-eight hours and thereafter the patient was catheterized for residual urine until this had fallen below 4 fluid ounces (115 ml.).

All cases of pyrexial urinary infections were excluded from the series and wound infection was considered to be present if the temperature rose above

100.4°F. (38°C.) on any one occasion after the first twenty-four hours following operation. A profuse purulent vaginal discharge irrespective of pyrexia was also accepted as evidence of vaginal infection. Antibiotics were not administered unless the temperature rose above 100.4°F. (38°C.), and only then after bacteriological sensitivities had been obtained. It soon became evident that hexetidine gel would not prevent the deep-seated cellulitis that often complicates vaginal hysterectomy and repair and these cases in addition received prophylactic streptomycin, 0.5 g. twice daily, and have been excluded from the series.

RESULTS

The results are summarized in tables I and II. From these it will be seen that the incidence of vaginal infection in the hexetidine group was 8 per cent. which compared favourably with 34 per cent. in the control group. There were no deaths in either group.

In the hexetidine group vaginal discharge was much less, primary union of vaginal mucosa was the rule and when the patients were examined six weeks after operation it was often difficult to see the scar, and infected granulation tissue was rarely seen.

SUMMARY

Hexetidine gel can be recommended as a safe and easily applied preoperative and immediate postoperative vaginal preparation in all cases of pelvic floor repair. The incidence of vaginal wound sepsis in the present investigation was reduced from 34 per cent. in the control group to 8 per cent. in the hexetidine group.

I wish to express my thanks to Mr. K. G. Seager and Mr. G. M. Evans on whose patients this trial was conducted and for the help and cooperation of the nursing staff of Farnborough Hospital. William R. Warner & Co. Ltd., supplied the hexetidine gel ('sterisil' vaginal gel) used in this trial.

References

Bowie, J. H. (1955): *Pharm. J.*, **74**, 473, 489.
Browne, A. D. H. (1955): *J. Obstet. Gynæc. Brit. Emp.*, **62**, 928.
Champ, C. J. (1955): *Ibid.*, **62**, 924.
Edwards, R. B., Church, B. D., Dukes, C. D., and Sander, R. G. (1956): *Bact. Proc.*, **1**, 66.
Lunt, R. L., Dutton, W. A. W., Dewhurst, C. J., and Russell, C. S. (1957): *Lancet*, **i**, 1240.
Marbach, A. H. (1948): *Amer. J. Obstet. Gynec.*, **55**, 511.

STRUGGLES WITH STRONGYLOIDES

By E. Ll. LLOYD, M.B., CH.B., D.T.M. & H.
Junior Hospital Medical Officer, Tropical Diseases Unit, Eastern General Hospital, Edinburgh

LARVÆ of *Strongyloides stercoralis* were often found alongside ova of hookworms in specimens of stool from patients in West Africa, and a beginner could mistake them for larvæ of hookworms. They were useful for impressing a patient whose one ambition was to have an injection of N.A.B., the drug in use formerly against yaws. He cared nothing for the hookworm ova pointed out to him down the microscope, but the Strongyloides larva, a writhing snake, made him exclaim 'Hey' and accept cure for the hookworms that were making him anæmic.

TRIAL BY ERROR

No cure was known for Strongyloides infestation, and it was counted trivial until ex-prisoners of war (Japanese) began to complain of a creeping eruption blamed on the migrating larvæ and making them scratch. Gentian violet was used by mouth or by vein with no clearance of the larvæ or of the urticaria but with blocking of the veins. When pension claims were discussed, those ex-prisoners of war who had no strongyloidiasis said the scratching did not matter, those who had it thought differently. Assurance by a consultant that anxiety neurosis was all that was wrong brought no relief. Effective treatment was sought. Ethyl chloride spray and mepacrine, by mouth and by injection at the advancing head of the creeping eruption, failed, though the scars from the mepacrine commemorate the attempt. Piperazine citrate, useful against round- and thread-worms, and diethylcarbamazine, useful against filarial worms, failed. Dr. W. R. Duff, himself an ex-P.O.W., cleared one patient using methylene blue 2 grains (0.12 g.) thrice daily for one week. After Dr. Duff left, others were not cured, and one came back bashful from week-end leave because he had wet the bed blue.

DITHIAZANINE

At last in the Spring of 1958 the pharmacist brought round a notice of a broad-spectrum anthelmintic, dithiazanine, said to be effective against strongyloidiasis. So far, 27 patients (one twice) have been treated with it here. It turned their stools green, and for three of the twenty-one days' course, 200 mg. three times a day, larvæ still writhed actively in the verdure. After that they were not to be found, and any urticaria ceased. The work done by Swartzwelder *et al.* made it unnecessary to subject our ex-P.O.W.s to duodenal intubation, a stool free from larvæ and skin relieved from urticaria being accepted as evidence of success.

Patients treated in West Africa were under the care of the Church of Scotland; P.O.W.s here were under the care of Col. E. H. Vere Hodge, Sir Alexander G. Biggam and Dr. F. J. Wright. Dithiazanine was supplied by Messrs. Eli Lilly & Co. Thanks to them and to Miss I. E. Ingram, the Pharmacist, this note appears.

GENERAL PRACTITIONERS' FORUM

NIGHT CALLS IN A GENERAL PRACTICE

By ALFRED MODEL, M.D., D.P.M.
Stockport, Cheshire

At twelve o'clock on a Sunday night one winter a young man phoned, asking me to come at once to see his daughter, aged 12 months, who 'has a terrible cough and is nearly choking'.

When I arrived some twenty minutes later, the baby's father greeted me apologetically with the words: 'She seems to have settled down a bit, she has had a cough for two days'. There was no history of loss of appetite, vomiting or any indication of real distress. On examination I found a healthy-looking little girl with a normal temperature, and the only positive finding was a mild pharyngitis. I did not know this family, and when I told the parents that there did not seem any cause for worry, the mother quickly said: 'I think she caught a cold in the nursery, and they did not tell me', adding that Denise, their only child, had been in the nursery for a week. I remember noticing that the living room was untidy.

Mrs. A. continued to talk, with little encouragement from me. The birth had been normal. 'I did not breast feed her; I had plenty of milk, but Denise does not like milk'. She also told me that she had started to go out to work a week ago, saying at first that they felt it would be good for the child to have company: 'I do not like spoilt children'. A little later she added: 'To tell you the truth, I feel hemmed in, I used to work on a farm'. I resisted the temptation to suggest that the mother should give up her job and look after her baby, though I permitted myself to say that being in a nursery did not suit all babies, adding tentatively that perhaps Denise was one of those children who needed to be with her mother more. I complimented Mrs. A. on her daughter's development so far and suggested she should watch out for signs that Denise was missing her.

I was not able to follow up this case, as the family were patients of another doctor in the district, but I have described it as one of a series I wish to discuss, as I have been interested for some time in the motives that lead a patient or relative to call their doctor at night.

SCOPE OF INVESTIGATION

I have therefore recorded the visits I did between the hours of 8 p.m. and 8 a.m. for a period of eighteen months. The practice, which consists entirely of N.H.S. patients, covers an area which is almost wholly industrial and lower middle class. Together with my partner we have a total of 4,500 patients on our list. We take night calls in alternate weeks, with the exception of one night, when the calls are taken by a neighbouring practice of similar size consisting of two doctors with whom we have a reciprocal agreement for another night. This same arrangement operates at weekends, so that each of the four doctors is on duty on one out of four weekends.

Making allowances for holidays and other domestic arrangements, in the eighteen months under review I was on duty on 198 nights, and I had altogether 94 calls, 71 of which were for our own patients; five patients

sent for me twice. There was no significant sex difference, if one deducts the obstetrical cases, and no seasonal variation (table I).

EMERGENCIES

I have been concerned to discover how many of my visits were for 'emergencies'. For the purpose of this investigation I have defined as an 'emergency' a condition in which there is danger to life or a risk of damage to health without immediate treatment, and/or where there is a degree of

Year	Jan.	Feb.	Mar.	April	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
1957	—	6	6	5	7	7	5	—	10	4	3	5
1958	2	5	4	5	1	4	5	—	10	—	—	—

TABLE I.—Monthly incidence of night calls.

physical or mental discomfort which requires intervention of a kind which only a doctor can be expected to provide, and here I agree with Ollerenshaw (1958) that serious organic disease is not a necessary component of a medical emergency. I am, of course, aware that there is a subjective element on the

Illness	All calls	Emergencies	Emergencies / All calls
Acute infectious diseases	29 (30.9%)	11 (22.4%)	37.9%
Cardiovascular	15 (16.0%)	12 (24.5%)	80%
Obstetric	10 (10.6%)	8 (16.3%)	80%
Psychiatric	14 (14.9%)	2 (4.1%)	14.3%
Accidents	6	4	
Abdominal	4	2	
Urinary	2	2	
Central nervous system	4	3	
Chronic respiratory	4	2	
Miscellaneous	6	3	
Total	94	49	

TABLE II.—Distribution of night calls according to diseases. Comparison between 'all calls' and 'emergencies'.

part of the doctor in such an assessment, and the picture is continuously changing as a result of advances in medical knowledge. I estimated that 49 of the 94 calls came within this category of emergencies, i.e. 52 per cent. (table II).

From these figures it emerges that the most frequent visits (30.9 per cent.) were for acute infections, most of which were diseases of the respiratory tract. This group, together with the cardiovascular and obstetrical conditions, accounts for more than half of my calls. In the 'emergency group' the cardiovascular conditions were the most common (24.5 per cent.), but in my small series such a finding will have to be treated with reservation. I was surprised to find that abdominal emergencies occurred relatively infrequently. In the eighteen months I did not see a single case of appendi-

citis, intestinal obstruction, or perforated peptic ulcer at night. The most significant difference between 'all calls' and 'emergencies' occurred in the group of psychiatric conditions. I have limited this group to patients who showed overt symptoms of mental illness (e.g. a case of paranoid schizophrenia, one of acute mania, a senile hypochondriasis, a post-traumatic anxiety state), and to patients who showed no signs of organic disease, and where a call at night could only be understood in terms of anxiety, guilt or hostility in the patient himself or the relative who sent for me. It is, of

Time	All calls	Emergencies
8-10 p.m.	41 (43.6%)	21 (42.9%)
10 p.m.-midnight	28 (29.8%)	12 (24.5%)
Midnight-2 a.m.	11 (11.7%)	7 (14.3%)
2-4 a.m.	3 (3.2%)	1 (2.0%)
4-6 a.m.	3 (3.2%)	3 (6.1%)
6-8 a.m.	8 (8.5%)	5 (10.2%)
Total	94 (100%)	49 (100%)

TABLE III.—Time distribution of night calls (see also fig. 1).

course, obvious that these mechanisms have been important, if not determining, factors in 'sending for the doctor' in many other cases and to some extent are responsible for the difference between the two groups, although I would add that relative ignorance, limited intelligence and social con-

Time	Acute infection		Cardio-vascular		Obstetric		Psychological	
	A	E	A	E	A	E	A	E
8-10 p.m.	15	6	6	3	3	3	9	1
10 p.m.-midnight	8	2	3	3	1	1	5	1
Midnight-2 a.m.	2	1	5	5	1	1	0	0
2-4 a.m.	0	0	0	0	2	1	0	0
4-6 a.m.	0	0	0	0	2	2	0	0
6-8 a.m.	4	2	1	1	1	0	0	0
Total	29	11	15	12	10	8	14	2

TABLE IV.—Time distribution of night calls in different illnesses. A=all calls. E=emergency calls.

ditions are additional factors. The visit mentioned at the beginning of this article is a clear example of a case in which a young couple try to seek relief from their anxiety and guilt by appealing to the doctor as a father figure.

Sometimes one is aware that an illness raises anxiety which can only be understood on the basis of the patient's medical history. During a recent influenza epidemic I was called to a man aged 45 with mild symptoms of influenza. His condition in itself did not justify a call at 6 a.m., and it was only with the knowledge that he had had an orchidectomy for a seminoma six months previously that I could understand the patient's anxiety.

Not only the patient but other members of the family bring to an emergency their own problems and fantasies.

John, aged 12, phoned at 11 p.m. and requested me to come to his mother who had had 'another stroke'. The patient had suffered from a hemiplegia following the birth of a daughter six years previously. When I arrived, Mrs. B. was in a deep coma, obviously suffering from a cerebral vascular catastrophe, and I remained until she died an hour later. During this time Mr. B. told me that shortly before his wife became unconscious John had complained of being thirsty, and his wife, who had told the boy several times to go to bed, had shouted at him and exclaimed: 'You are worse than James!' (a cousin who had died with a chronic nephritis). While I was in the house, John and his father asked me several times whether I thought that this row could have caused the stroke. In spite of my categorical denial John has shown signs of considerable guilt over his mother's death, a feeling which he finds so hard to bear that he is now dealing with it by blaming me. He recently said: 'The other time the doctor saved her, why didn't you do more?'

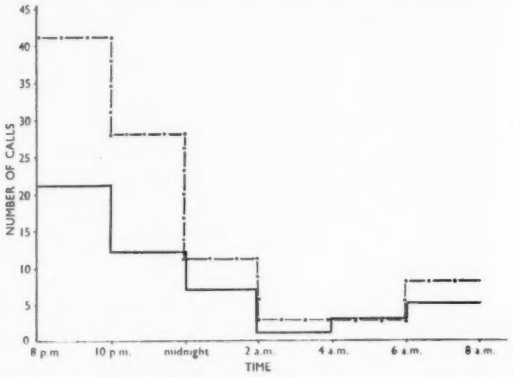


FIG. 1.—Time distribution of night calls (— · — · — · = all calls; ——— = emergency calls).

One cannot know with certainty what was behind the mother's remark and one cannot know the ultimate outcome of the boy's guilt. Such pieces of family history which one meets constantly, particularly in a crisis, as during a night visit, become part of the family doctor's store of knowledge. They can be invaluable at a later stage in helping to understand some aspect of a patient's behaviour.

We are all aware of our subjective reaction to a call at 4 a.m. as compared to one at 10 p.m., and I have examined the series with the aim of assessing the nature and frequency of calls occurring before and after midnight (tables III, IV; fig. 1). It emerges that most calls (73.4 per cent. of all calls and 67.4 per cent. of emergencies) came before midnight. Few occurred between 2 a.m. and 6 a.m.: only six during the period under review (6.4 per cent.). One may perhaps be justified in inferring that once sleep is firmly established, it is less likely that the patient will wake up again and need medical help.

THE EFFECT OF AGE

The age of the patients was divided into 15-year groups (tables V, VI; fig. 2) If calls for abortions and confinements are deducted, it is seen that the young adult hardly ever needed to be visited at night. As would be expected, cardiovascular diseases required visits mainly after middle age and increased

rapidly with increasing age. Among the older patients a comparatively high percentage (76.2 per cent.) of the visits were for 'emergencies'. Most acute infections occurred in early childhood (52 per cent.). With the child parents sought medical advice for conditions which in older people would often have been dealt with in another way. In the 'all calls' group there was a peak in middle age which is largely due to the fact that night calls for psychiatric conditions were comparatively common in this age-group. We know, of course, that middle age is the peak period for involutional melancholia, but it is of interest that of the eight psychiatric calls in the age-group, 31 to 60 years, only one had primarily depressive symptoms. In five of the remaining cases the outstanding factor appeared to be inadequacy of the patient's personality, and the precipitating factor for the call was a transitory anxiety attack. (A middle-aged solitary bachelor who got the neighbours to send for me because of a heavy thunderstorm.) The series is completed by one case of paranoid schizophrenia and one of acute mania. There was no sex difference in this small group.

Age in years	All calls	Emergencies
0-15	21 (22.3%)	6 (12.2%)
16-30	15 (16.0%)	9 (18.4%)
31-45	23 (24.5%)	9 (18.4%)
46-60	14 (14.9%)	9 (18.4%)
60+	21 (22.3%)	16 (32.6%)
Totals	94 (100%)	49 (100%)

TABLE V.—Age distribution of night calls (see also fig. 2).

Age in years	Acute infections		Cardio-vascular		Obstetric		Psychiatric	
	A	E	A	E	A	E	A	E
0-15	15 (52%)	6 (54%)	0	0	0	0	2	0
16-30	2	0	0	0	8	6	2	0
31-45	6	1	1	1	2	2	8	2
46-60	4	2	3	3	0	0	0	0
60+	2	2	11	8	0	0	2	0
Total	29	11	15	12	10	8	14	2

TABLE VI.—Age distribution of night calls in different illnesses. A=all calls. E=emergency calls.

SOCIAL FACTORS

Whether these findings have a wider application, will only emerge when a longer period has been studied, and it would be interesting to compare them with similar studies in other practices. Social factors must be taken into consideration in a survey of this kind. For example, the availability of the telephone could operate both ways: in a middle-class practice it could lead to more frequent calls and fewer visits. Economic and social factors enter into the picture constantly.

Last July I was called at 9.15 p.m. to a 17-year-old boy of good physique. On my arrival his mother said: 'Sorry to call you so late, I have never called a doctor in the evening before, but Peter has been ill for two days, and I wanted to make sure whether I could go to work tomorrow'. My first reaction was irritation, and I said: 'Well, if you are so worried about him now, I can't see how you can leave him tomorrow'. Mrs. D. did not respond to this criticism but, when I had confirmed that her son had only a mild attack of tonsillitis, her reproach came when she said: 'You remember his father?' As soon as she spoke, I recalled that her husband had been killed in a traffic accident, and she had been unable to obtain compensation; so her need to go out to work was understandable.

Looking at this case in retrospect I can well imagine that for two days the mother could go to work and allow her son to stay at home without

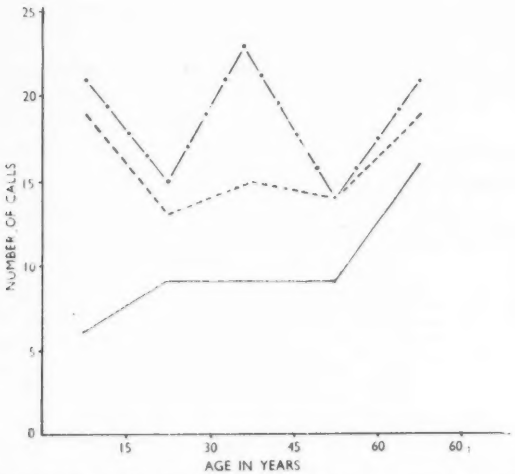


Fig. 2.—Age distribution of night calls(_ . _ . _ . _ = all calls; ——— = emergencies; - - - - - - = all calls without psychiatric cases).

becoming too anxious. He was obviously an independent young man. But after two days, with little improvement in his condition, she suddenly felt anxious and guilty, and as a further justification for her anxiety she had commented to me: 'I was worried, because he had scarlet fever quite badly as a boy, and it started the same way'. Thus, this widow's call became understandable. This case also brings out another problem of which we are often aware when called at night: i.e. the delay between the onset of the illness and the request for a visit. With this boy the delay seemed to be primarily due to a social factor, the mother's need to go to work, but I think one should add that the other motives mentioned as being responsible for the non-emergency call (anxiety, guilt, hostility, relative ignorance, and limited intelligence) may also account for these delays. Whilst over-anxiety may produce an 'unnecessary' call, such a feeling can in some cases lead to a delay which can only be understood in terms of the individual's

fear of the diagnosis. We are all familiar with the patient who postpones a consultation for a suspected cancer.

Among the cases included in this series is that of a child whose symptoms were highly suspicious of poliomyelitis, and where I was not sent for until these symptoms had been present for three days. To the 'fear of knowing' was added the guilt of responsible parents who had chosen not to have their child immunized. Twenty years ago this story could have been told with diphtheria as the dreaded illness.

A PARENT FIGURE

It has been commented on before (Balint, 1957; Model, 1957), and my experience with night calls emphasizes again the observation that the family doctor is often appealed to as a parent figure. Indeed, with night calls one is reminded of the child who wakens at night and shouts for his mother. Just as parents reach the limit of their patience when these demands become too frequent and their otherwise self-reliant six-year-old calls for a drink of water for the third time, so we too may become aware of some irritation. I cannot speak for all of us, but I think many would agree that first comes the urge to ignore the telephone bell, and then irritation. The extent to which we can accept this feeling as something within us instead of projecting it on to the patient may be a measure of the extent to which we can be objective by the time we have reached the patient. If in the first case quoted I had projected the cause of my annoyance on to those young parents and taken their call for help as 'unreasonable' or 'a waste of time', I would not have been able to see that it was their guilt that was responsible for their call. If I had reproached them, their feeling that they were incompetent parents would have been strengthened.

CONCLUSION

A survey of the literature reveals great disparity in the attitude of the authors towards night calls.

Hartsilver (1951) considers that '. . . 99 per cent. of all night calls have proved unnecessary . . . '. He suggests that patients who 'refuse to fall into line should be recommended to change their doctor . . . '. Pinsent (1954) considers that 'the number of panic calls can be greatly reduced by a consistent process of education . . . ' (see also McGregor, 1950). Taylor (1954) finds that '. . . patients are now very considerate over making night calls', and he suggests that 'it is the doctor's duty to respond to a night call, no matter how frivolous it may appear . . . '.

Stamm (1955), of Jamaica, and Forbes (1955), of Massachusetts, have published detailed analyses of their night calls but, so far as I have been able to ascertain, of authors working in this country only Fry (1952) has published accurate figures for his practice. If allowances are made for the visits made as a result of the rota arrangement in our practice, his figures and mine appear to correspond fairly closely: 2.5 per cent. of his patients needed to be visited at night; my figure was 2.9 per cent. a year. The decision to make a study of any specific problem has its effects on the investigator's attitude.

In the past eighteen months I have found night calls less irksome, a by-product which will have been noted by workers in other fields.

I would like to thank the Library of the Royal Society of Medicine, for supplying me with some of the references, and also Dr. M. Bulmer, of the Department of Social and Preventive Medicine, University of Manchester, who discussed this article with me.

References

Balint, M. (1957): 'The Doctor, His Patient and The Illness', London.
Forbes, W. (1955): *New Engl. J. Med.*, **253**, 60.
Fry, J. (1952): *Brit. med. J.*, **ii**, 249.
Hartsilver, J. (1951): *The Practitioner*, **166**, 394.
McGregor, R. M. (1950): *Edinb. med. J.*, **57**, 433.
Model, A. (1957): *Brit. J. psychiat. soc. Work*, **4**, 4.
Ollerenshaw, J. G. (1958): *Proc. Roy. Soc. Med.*, **51**, 443.
Pinsent, R. J. F. H. (1954): In 'Clinical Medicine in General Practice', edited by J. Fry, London.
Stamm, H. (1955): *West Indian med. J.*, **4**, 212.
Taylor, S. (1954): 'Good General Practice', London.

JACK THE BABOON

By R. N. WOODSEND, M.B., B.S.
Catterick, Yorkshire

It was a lovely July day. Two girls, final-year students, had been with us for a week's experience of country practice and Dr. Pickles had kindly asked us over to Aysgarth to see the records of his practice in the Dales. We had a most enjoyable drive through Wensleydale and a typical Yorkshire welcome by Dr. and Mrs. Pickles. The afternoon passed quickly inspecting the records and discussing epidemiology in the Yorkshire Dales. After tea Dr. Pickles produced his day book in which were recorded, for many years, humorous or extraordinary happenings on his daily rounds. There was a pause in the conversation and I tried to fill the gap.

'A QUEER PATIENT'

My most interesting and important patient was not a human but a baboon, Jack by name, the mascot of the South African Brigade. It was April 1918, when the Germans had advanced beyond Passchendaele and Mont Kemmel and our Brigade H.Q. had withdrawn to behind Rinningholst, a small camp of wooden huts alongside the main road. The troops, including the South African Brigade, were retreating down the road which was shelled all the morning. I felt that I should be happier to be busy, so when a veterinary officer asked me to see a queer patient that had been brought to him it was a relief. It was a pathetic sight; the little fellow, carried by his keeper, a corporal, lay moaning in pain, the corporal crying his eyes out in sympathy. 'You must do something for him, he saved my life in Egypt, he nursed me

through dysentery'. It seemed that the baboon was a most intelligent animal, drilling and marching with the troops. He was badly wounded, the left leg hanging with shreds of muscle, another jagged wound of the right arm.

'ON THE STRENGTH'

We decided to give the patient chloroform and dress his wounds; if he died under the anæsthetic perhaps it would be the best thing: as I had never given an anæsthetic to such a patient before, I thought it would be the most likely result. However, he lapped up the chloroform as if it had been whisky, and was well under in a remarkably short time. It was a simple matter to amputate the leg with scissors and I cleaned the wounds and dressed them as well as I could. He came round as quickly as he went under; the problem then was what to do with him. This was soon settled by the corporal: 'He is on the strength'. So duly labelled, number, name (Private Jack), A.T.S. injection, nature of injuries, etc., he was taken to the road and sent by a passing ambulance to the C.C.S. It was several days before I could visit the C.C.S. 'Oh, yes', said the C.O., 'he was pretty bad when he arrived, but we put him to bed and that night when I was doing the rounds he sat up in bed to salute me. He went down to the base hospital next day'.

OFFICIAL RECOGNITION

About three weeks later when *The Times* of April 22, 1918, reached us, I read that the most curious patient at the base hospital was my baboon, 'a most amenable and gentle patient':—

> 'A curious detail of the casualties', said the special correspondent of *The Times*, 'is that in one of the base hospitals now there lies in (or at least on) a bed, with other honourably wounded heroes, one Jack the Baboon, the mascot of the South African Brigade. He lost a leg and is wounded in one arm, but he has stood an operation and treatment well, and is said to be a most amenable and gentle patient'.

When he was convalescent he used to play with the soldiers on the beach, and always struggled up to salute any passing officer. Some time later I was sent a cutting from a Leicester newspaper, an account of a Red Cross fete at which my baboon appeared—2*s.* 6*d.* for a handshake and 5*s.* for a kiss. At the end of the War he had a special carriage in the Lord's Mayor's Show, and on his return to South Africa was the centre of attraction in the Victory Parade and welcome home of the South African Brigade.

I never heard more, but have often wondered what became of him. Did he live to a great age, was he pensioned off, or did he remain to the end the mascot of the South African Brigade?

EPILOGUE

So ended my contribution to the afternoon's meeting. To my surprise Dr. Pickles insisted that I should write the story for publication and, being naturally weak-willed, I have done so.

SECTIONS OF GENERAL PRACTICE AND ENDOCRINOLOGY
OF THE ROYAL SOCIETY OF MEDICINE

DISCUSSION ON THE DIAGNOSIS OF THYROID DISEASE

March 18, 1959

Dr. James Crooks (*Western Infirmary, Glasgow*).—Thyrotoxicosis occurs more commonly in women and often a family history of thyroid disease can be obtained. I consider that Graves's disease and toxic nodular goitre are different phases of the same disease and the higher incidence of cardiac complications in the latter can be accounted for by the older age-groups affected.

A survey of the frequency with which the clinical features of thyrotoxicosis occurred in thyrotoxic patients, euthyroid patients initially suspected of having thyrotoxicosis, and normal control subjects has been previously reported (Wayne, 1954). Using this information, scores were allocated to the clinical features of the disease, based on their diagnostic value, and in a large series of cases the clinical diagnostic index so derived correlated well with the final diagnosis and the results of laboratory tests (Crooks, Murray and Wayne, 1959).

HYPOTHYROIDISM

A survey of the clinical features of hypothyroidism has been carried out in 100 cases of the primary condition, 50 cases of secondary hypothyroidism induced by therapeutic measures for thyrotoxicosis, 55 normal subjects, and 15 patients with panhypopituitarism. In primary hypothyroidism the most important diagnostic features were lethargy, slow movements, hoarseness, paræsthesia, intolerance of cold weather, untidy hair, periorbital puffiness, and cold, dry skin. Weight gain was usual and paræsthesia, often due to the carpal-tunnel syndrome, was present in more than half of the cases. In secondary hypothyroidism produced by over-treatment of thyrotoxic patients there was a much bigger incidence of muscle pain, and deafness was relatively less frequent. It is probable that such differences in the symptomatology are due to the more rapid onset of thyroid hormone deficiency in therapeutically induced hypothyroidism.

In the case of panhypopituitarism symptoms and signs due to diminution in the amount of circulating adrenocortical or gonadal hormones often dominate the clinical picture but sometimes cases resemble primary hypothyroidism very closely. In this variety of secondary hypothyroidism the skin manifestations of thyroid hormone deficiency are less striking than in primary hypothyroidism and the physical signs of myxœdema, such as

puffiness of the periorbital tissues, supraclavicular fossæ and the wrists, are much less common. Recognition of this type of hypothyroidism is important since the administration of thyroid preparations may precipitate acute adrenal insufficiency.

HASHIMOTO'S THYROIDITIS

Hashimoto's thyroiditis was until recently regarded as a rare condition but the development of tests for detecting circulating antibodies to thyroglobulin has shown that the condition is not uncommon. The diagnosis should be considered whenever a middle-aged woman presents with a goitre, especially of recent development, of moderate size, and firm in consistency. Many cases show evidence of hypothyroidism and the clinical diagnosis of Hashimoto's thyroiditis would be made more often if the neck were carefully palpated for a goitre in all hypothyroid patients. Operation is not usually necessary and the administration of *l*-thyroxine sodium will cause the goitre to diminish in size as well as relieve the symptoms of hypothyroidism if they are present.

CARCINOMA OF THE THYROID

Carcinoma of the thyroid is a relatively rare condition. About one-quarter of the cases have undifferentiated carcinomas which are highly malignant and are usually in the older age-groups. About half the cases have a papillary adenocarcinoma which is a relatively benign neoplasm which metastasizes locally. The follicular adenocarcinoma, which is less common than the other thyroid neoplasms, tends to metastasize early and widely and is often so well differentiated that it may take up radioactive iodine in sufficient quantity for it to be used therapeutically.

References

Crooks, J., Murray, I. P. C., and Wayne, E. J. (1959): *Quart. J. Med.*, **18**, 1.
Wayne, E. J. (1954): *Brit. med. J.*, **i**, 411.

Dr. David Wheatley (*Twickenham, Middlesex*).—Hyperthyroidism is easier to diagnose than hypothyroidism in general practice as the presenting symptoms are nearly always more obvious. On the other hand, myxœdema, which may be partial, particularly in old people, may easily be missed by the general practitioner. The insidious onset of the typical myxœdema facies can be missed, when the patient is seen frequently, although the diagnosis may be obvious to a consultant seeing the patient for the first time. An examination of the records in my own practice has revealed a total of nine proven and four suspected cases of myxœdema. In contrast, there are only records of five cases of hyperthyroidism and two cases of non-toxic adenoma. The incidence is almost entirely female, there being only one male case in all these cases of thyroid disorder: a case of myxœdema.

The commonest presenting symptom was increase in weight, other symptoms occurring relatively infrequently and varying from patient to patient.

Increase in weight was present in seven out of nine proven hypothyroid cases. The typical facies was present in all cases. The other common manifestations of thyroid under-activity were inconstant and varied from case to case. The more elaborate investigations are not possible in general practice. Although at this stage cases can be referred to hospital, if the general practitioner wants to study them further he must proceed without handing over control of the case to the hospital consultant. The serum cholesterol is a useful investigation, when it is markedly elevated and when it falls promptly with the exhibition of specific therapy. The B.M.R. was only done in one case, owing to the difficulty of readily obtaining this investigation. Electrocardiography was performed in several cases, but in only two were typical changes found; these responded to treatment with thyroid.

Response to treatment is a valuable confirmatory factor in the diagnosis of the condition. In the cases under consideration the usual result was the achievement of a normal appearance, which occurred in every case. Weight loss also is a constant feature of treatment with thyroid in this condition and the other typical signs and symptoms, when present, also reverted to normal. The cholesterol level reverted to normal in those cases in which it was raised and there was also a fall in blood pressure and reversion of anæmia to normal following treatment with thyroid.

Dr. Alastair G. Macgregor (*University of Edinburgh*).—We have at our disposal a number of different tests of thyroid function, each measuring a different facet of the activities of the gland.

THE DIAGNOSIS OF THYROID DISEASE

The impact of the hormone on the body cells, and the resultant consumption of oxygen by the tissues, are measured by the basal metabolic rate. The isotope tests all measure the dynamic activity of the thyroid gland, by making it possible to observe the way in which the thyroid handles iodine, one of the basic components of thyroid hormone. The protein-bound iodine (P.B.I.) gives a direct index of the hormonal output of the thyroid gland. Both groups of tests are dependent upon the fact that the molecule of thyroxine contains four atoms of iodine. The isotopes label iodine in the hormone, and the various sequential steps that occur in the manufacture of the hormone can be followed by physical means. The chemical P.B.I. determination measures the iodine in the serum that is derived from thyroid hormone. The amount of radio-iodine absorbed by the gland is proportional to the activity of the thyroid and, within limits, a reciprocal measure of gland activity is given by the amount excreted in the urine. In the normal individual there is an approximately even division of radio-iodine between gland and urine, but in hyperthyroidism there is an early and much greater absorption of radio-iodine into the thyroid, and proportionately small amounts excreted. In the non-functioning gland in hypothyroid states the

majority of the administered isotope can be recovered in the urine.

The precise test carried out depends upon the individual preferences. Most centres use I^{131} as it is simple and easy to handle, but the short-life isotope, I^{132}, is more appropriate for use in young people and for repeated tests. Tests involving the use of I^{132} usually involve bringing patient and counting apparatus together for direct measurements. I^{131} makes it possible to collect urine and plasma samples in a laboratory many miles from the patient. Our practice derives from our experience over a period of some ten years (Macgregor and Wayne, 1958). The gland uptake after four hours is found to be over 45 per cent., and usually over 40 per cent., in thyrotoxic individuals.

The second test used in the diagnosis of hyperthyroidism is the level of protein-bound plasma activity after forty-eight hours (Goodwin *et al.*, 1951). Levels over 0.4 per cent. per litre are found fairly constantly in the presence of toxicity.

We apply the divided urine collection technique of Fraser *et al.* (1953) and calculate the T index. Sufficient diagnostic information can often be derived from analysis of the eight- to twenty-four-hour urine sample alone, the normal individual having radio-iodine contents during that period of 6 to 20 per cent.

With cooperation between laboratory and practitioner it is easy to devise radio-iodine techniques suitable for a given situation. We have active and flourishing arrangements with individual doctors and hospitals who regularly send aliquot urine samples or samples of plasma, after the administration of tracer doses of I^{131} to their patients. There is no reason why the use of simple isotope tests of this nature should not be greatly extended and become a more universal part of the laboratory services throughout the country.

We have been more fortunate in the use of the chloric acid protein-bound iodine technique than with previously used methods, but it requires meticulous attention to detail. On the other hand, it does give an accurate index of level of circulating hormone. In our hands levels below 3 micrograms per cent. indicate hypothyroidism, and above 7.5 micrograms per cent. hyperthyroidism, but there is a small number of equivocal results in both cases. One of the most useful applications of the technique is in the control of treatment.

The most important fallacy regarding thyroid function tests is the previous use of iodine-containing drugs or radiological contrast media which can vitiate tests for many months.

TREATMENT

In the great majority of instances of hypothyroidism the use of dried thyroid is the most successful treatment but in a proportion the non-absorption, or inactivity, of the tablets leads to difficulties. The substitution of thyroxine for the thyroid results immediately in improvement. There is now no

tenable argument for continuing to use thyroid tablets instead of pure thyroxine. The latter drug is not significantly more expensive.

References

Fraser, R., Hobson, Q. J. G., Arnott, D. G., and Emery, E. W. (1953): *Quart. J. Med.*, **22**, 99.

Goodwin, J. F., Macgregor, A. G., Miller, N., and Wayne, E. J. (1951): *Ibid.*, **20**, 353.

Macgregor, A. G., and Wayne, E. J. (1958): In 'Modern Trends in Endocrinology', edited by H. Gardiner-Hill, London, chapter 4.

Dr. D. N. Barron (*Royal Free Hospital, London*).—'Basal metabolism' means the metabolism measured under standard fasting and resting conditions, for muscular activity, digestion of food, and excitement all increase calorie output. Unless these precautions are observed, the patient will not be 'basal' and the oxygen consumption will be too high. The oxygen consumed is converted to calorie output by factors. The calorie output/M^2 surface area/hour is then expressed as the percentage which it is above or below that of normal subjects. The results given here are related to Aub/du Bois standards. The normal range with this method in this series of 110 normals is +6 per cent. to −19 per cent. The standards of Robertson and Reid have replaced those of Aub and du Bois during the last five years, giving a normal range of +13 per cent. to −13 per cent.

In thyrotoxicosis the B.M.R. is raised: in 110 cases it ranged from ±0 per cent. to +71 per cent., the average being about +30 per cent.; nine cases were within the normal range. The value of the B.M.R. is proportional to the clinical toxicity: on successful treatment, the B.M.R. returns to normal for that patient. Although a high B.M.R. is found in a number of other diseases, they are not those which generally present any problem of differential diagnosis. Any disease in which there is increased metabolism, including fever, or tissue breakdown, may give a high B.M.R., but not usually above +20 per cent. A disorder where differential diagnosis from thyrotoxicosis may be needed is 'anxiety state'. The B.M.R. of such patients is not reduced by a short course of iodine, but is reduced by mild sedation.

In myxœdema the B.M.R. is lowered: in 110 cases it ranged from −14 per cent. to −45 per cent., the average being about −30 per cent.; six cases were within the normal range. As the patient is successfully treated by thyroid hormone, so the B.M.R. returns to the patient's normal. A low B.M.R., which is rarely below −30 per cent., can be found in a variety of other conditions which are included in the general classification of reduced activity, reduced intake of food and other endocrine deficiencies. The B.M.R. of a primary or secondary hypothyroid patient will be raised by thyroid but not the B.M.R. of hypometabolism from other causes.

B.M.R. estimation is an accurate measure of the general metabolic state of a patient. Its value is as a measure of the severity of metabolic disturbance in thyrotoxicosis or myxœdema, and it is useful in differential diagnosis.

SOME MORE 'DISABLED' SPORTSMEN

By H. J. C. J. L'ETANG, B.M., D.I.H.

DOCTORS are trained to detect disabilities, and in assessing these, may forget other inherent or acquired abilities possessed by the patient. In 1955, I described some of the disabled who had succeeded in first-class competitive sport[1] and it seemed that they were the gallant exceptions. Further study has shown that disabilities of varying degree are relatively common in first-class sportsmen, as indeed they are in the population as a whole.

EYES

In the earlier article I mentioned some spectacled cricketers, and in 1953 a whole team of such men could have been assembled from first-class cricketers[2]. Two ophthalmologists, F. W. Law and M. J. Roper-Hall, consider that visual acuity is not vital in ball games, with the possible exception of tennis, and that the important factor is one of coordination between the visual centres, the body musculature, and the centres of equilibrium[3]. It is of interest that Sir Donald Bradman's visual acuity and reaction times when tested in the laboratory were no better than the average university student. The importance of coordination is further illustrated by another Australian cricketer, W. H. Ponsford, once called the 'batting machine'. If visual acuity were vital, the fact that he was red-green colour blind should have proved a handicap[4].

Drobny is another example. He first noticed failure of vision following a head injury, and after 1939 wore glasses for tennis, and eventually became Wimbledon champion in 1954[5].

The modern athlete can be fitted with plastic lenses, and their value was proved during the British Lions Rugby Tour of South Africa in 1955. D. G. S. Baker, the utility man, always used them[6], but one of the three-quarters, though so advised, was not fitted with them. In the last test match, this particular three-quarter twice fumbled high kicks, and on each occasion the Springboks scored[7].

EARS

Defective hearing is not a handicap in a sport such as boxing, and Mario d'Agata, an Italian deaf mute, won the bantam weight championship of Europe in 1955.

It may be a disadvantage at cricket, as was shown in the first Test Match between England and Australia in 1953. Tallon, the Australian wicket keeper, was deaf, and as he went into bat, his Captain who wanted him to appeal against the light and stop play said 'Have a go for the light, Deafy'. Tallon, who only heard the first three words, hit out, and quickly lost his wicket, much to his captain's wrath.

Deafness was a boon to one player during the rugby game between France and Scotland in Paris in 1913, which is still referred to as the riot match. The crowds were so threatening that mounted cavalry were called to the ground. As the Scotsmen apprehensively hastened from the field, with the crowd baying for their blood, Dickson, the Scottish full back, who was deaf, observed that the crowd were taking the French defeat in a really sporting manner![8].

UPPER LIMB

Current conceptions of disability must surely be revised after consideration of Harold V. Connolly, and Joe Black. Connolly has a left brachial plexus palsy caused by birth injury. In addition to muscular paralysis and wasting, there are sensory and trophic disturbances. Despite these, he established a new world record in 1956, throwing the 16 pound (7.25 kg.) hammer 224 feet 10½ inches (68.5 metres)[9]. Black used to pitch for the Brooklyn Dodgers. The extensors of each of his index fingers are paralysed, and he has to slip his thumb under the index finger to lift it. As a result he can pitch a fast ball and an orthodox curve, but not a slow ball or a knuckle ball. He was not as lucky as 'Three Finger' Brown who pitched for the Cubs before the 1914-18 War. He had lost the first joints on his right index and middle fingers, but his strange grip on the ball enabled him to pitch an unusual curve which puzzled batters[10].

It is possibly easier for an established player to adapt his play to a disability. In the early 1920's, Tilden lost the tip of a finger in his right hand, but altered his grip, without affecting his play[11]. In contrast, it is amazing that Hilde Sperling could grip a tennis racket at all. The little and ring fingers of her right hand were flexed at a right angle to the palm, following an accident in which the tendons were cut[12].

A most remarkable adaptation was made by Karoly Takacs, who first represented Hungary at pistol shooting in the 1936 Olympic Games[9]. In 1938 he was involved in an accident which resulted in a mid-forearm amputation of his right arm. Takacs decided to continue pistol shooting using his left arm, and as early as 1939 won the world championship. He won Olympic Gold Medals in 1948 and 1952.

LOWER LIMB

During the 1939-45 War, many potential champions must have sustained gun-shot wounds, and the subsequent careers of three such men are of interest, since they were all wounded in the leg. Yvon Petra was wounded in the leg in 1940, and at one time an amputation was contemplated. He overcame the disability sufficiently well to become the first post-war Wimbledon tennis champion in 1946[11, 13]. Dalzell, the New Zealand rugby forward, was wounded in the leg by a bomb while serving in the Pacific, and was discharged from the Army. Subsequently he played rugby football for New Zealand and scored the only (and winning) try against England

in 1954[14]. Lou Brissic, who played baseball for Philadelphia Athletic in 1947, had a leg wound, and covered the shell-damaged area with a plastic guard[15].

In my previous article I mentioned Glen Cunningham, the American mile champion. He was severely burned in childhood, lost some toes on the left foot, and for a time had a flexion contracture of the right knee. In the 1930's he participated in many races, inevitably called 'The Mile of the Century'. Two of his rivals had previously been injured. William Bonthron had had an electric burn of the left leg later treated by a skin graft, and Archie San Romano had 1½ inches (3.8 cm.) of shortening of the right leg as a result of a fracture in the region of the right hip joint[16]. Another American, the marathon runner Clarence de Mar, had a congenital deformity of one foot. For twenty-five years he never finished lower than third place in the Boston long-distance race[17].

Many people, even in England, regard cricket as an intolerably slow and dull game. They will not be surprised to learn that there has been a one-legged player in first-class cricket. A. D. Denton lost a leg in the 1914-18 War, but played four times for Northamptonshire in 1919, with a batting average of 22.33[18].

SOME SURGICAL CONDITIONS

Amateur athletes are anxious to return to their particular sport as quickly as possible, and their usual rapid return to full function after injuries or operations suggests that, in general, doctors may be far too cautious with their ordinary patients. Occasionally elaborate 'rehabilitation' is advised, but more usually there is a long period of 'light duties'. Within three weeks of an appendicectomy, A. G. A. Murray the South African 'all-rounder' played in a Test Match against Australia. He scored 17, and bowled 25 overs[19]. Early in 1953, that outstanding American woman athlete, Babe Didrikson, was found to have a carcinoma of the bowel, and a colostomy was performed. Three months later she played in the Tam O'Shanter All American Golf Championship. A year later she won the American Women's Open Golf Championship by 12 strokes[20].

SOME MEDICAL CONDITIONS

The success of certain sportsmen emphasizes the fact that therapeutic advances have altered the prognosis of some diseases. Many doctors still appear to think of the basic pathological abnormality, rather than of the improved bodily state produced by modern treatment. Appleyard, the Yorkshire cricketer, is an outstanding example. He was found to have pulmonary tuberculosis in 1952. After a course of chemotherapy and a surgical operation, he made a complete recovery and was one of the successes during the M.C.C. cricket tour of Australasia in 1954-55[21]. The outlook was much more uncertain for Alice Marble, the American tennis player, when a tuberculous pleural effusion was diagnosed in 1934, but she eventually

recovered her full health, and became Wimbledon champion in 1939[11, 12].

The maintenance of a sportsman with diabetes mellitus is an interesting problem, and the case of G. M. Woolf (known as the Iceman) must have been fascinating. He became the champion jockey of America, and the alterations in diet dictated by his occupation made his diabetes particularly difficult to control[16].

Other endocrine disorders present therapeutic problems, which apparently explains the conduct of the American tennis player, Bob Falkenburg, who became Wimbledon champion in 1948. His habit of sitting or kneeling on the court during a game led to much adverse criticism. It seems that he must have had a toxic goitre at the time, for he is described as having 'excessive thyroid' which made him sluggish and languid, and caused profuse perspiration, loss of stamina, and irritability[13].

Hæmophilia is a condition that many doctors only see in the examination hall. It is encouraging to think that it may be met on the golf course in the shape of the well-known American golfer Byron Nelson[22].

CONCLUSION

Every day, doctors in practice must give many certificates of disability. On certain occasions in the Courts, or at pension boards, they are asked to assess the degree of disability in special cases, in which there appears to be a price list for loss of a limb or an organ.

It seems that the threshold for 'disability' might be considerably raised. In view of the cases already quoted, can the conscientious doctor really say that loss or malfunction of a limb or special sense organ invariably leads to disability?

References

1 *The Practitioner* (1955): **174,** 584.
2 Weinstein, J. L., *The Cricketer*, August 22, 1953.
3 Meeting of the British Association of Sport and Medicine, October 1958.
4 Fingleton, J. H., 'Masters of Cricket'.
5 Drobny, J., 'Champion in Exile'.
6 Pignon, L., *Daily Sketch*, January 4, 1955.
7 Parker, A. C., 'Giants of South African Rugby'.
8 Sewell, E. H. D., 'Rugger, the Man's Game'.
9 Jokl, E. (1957): *J. Amer. med. Ass.*, **165,** 129.
10 Frank, S., *Saturday Evening Post*, April 4, 1953.
11 Brady, M., 'Centre Court Story'.
12 Jacobs, Helen, 'Gallery of Champions'.
13 Cutler, N., 'Inside Tennis'.
14 Hayhurst, J., 'The Fourth All-Blacks'.
15 Einstein, C., 'The Fireside Book of Baseball'.
16 Boynick, D. K., 'Champions by Setback'.
17 Davis, M., '100 Greatest Sports Heroes'.
18 *The Cricketer*, 1956.
19 Miller, K. R., and Whitington, R. S. (1953): 'Bumper'.
20 *Star*, November 27, 1956.
21 *Daily Express*, August 3-6, 1954.
22 Demaret, J., 'My Partner, Ben Hogan'.

CURRENT THERAPEUTICS

CXXXVIII.—KANAMYCIN

By ELLARD M. YOW, M.D.

Professor of Medicine, Baylor University College of Medicine, Houston, Texas, U.S.A.

THE increasing difficulties encountered in the treatment of infections due to resistant strains of such micro-organisms as the staphylococcus and many of the gram-negative bacilli have led to the intensification of efforts to develop new antibiotics active against these bacteria. The discovery of kanamycin is one of the most important results of this effort.

Kanamycin was isolated from *Streptomyces kanamycetus* by Umezawa at the Japanese National Institute of Health and Tokyo University in 1957. The original material contained two fractions, A and B, but the antibiotic now available is almost pure kanamycin A. The early *in vitro* and *in vivo* studies in Japan demonstrated that kanamycin was active against many gram-negative pathogens, against strains of staphylococcus resistant to other antibiotics, and against streptomycin- and isoniazid-resistant strains of *Mycobacterium tuberculosis*. Clinical studies were carried out initially on cases of pulmonary tuberculosis, but subsequent clinical reports showed the drug to be effective against infections due to a wide range of micro-organisms.

CHEMISTRY

Cron and his co-workers (1958) determined the chemical composition of kanamycin and showed that hydrolysis will yield 2-amino sugars linked glycosidically to 2-dioxystreptamine. The drug is water-soluble, stable through a pH range of from 2 to 11 under normal sterilizing conditions and at a boiling temperature for thirty minutes at a pH of 6 to 8. The structural formula resembles that of neomycin, in that there is a common dioxystreptamine moiety, but the two antibiotics differ in the amino sugars.

ANTIBACTERIAL ACTIVITY IN VITRO

Microbiological studies have revealed a wide spectrum of *in vitro* activity against the staphylococcus, the bacillus group, vibrio, salmonella, shigella, mycobacteria, the coliform group, and some strains of proteus and pseudomonas. The antibiotic is relatively inactive against most streptococci, pneumococci and most anaerobic organisms. The antibacterial action is primarily bactericidal in that the bactericidal concentration of the antibiotic is approximately equal to the concentration required to produce bacteriostasis.

Kanamycin exhibits complete cross-resistance to neomycin; that is, all neomycin-resistant and neomycin-sensitive strains of organisms are kana-

mycin-resistant and neomycin-sensitive strains are kanamycin-sensitive. There are, however, quantitative differences between the susceptibility of various micro-organisms to kanamycin and neomycin, neomycin generally being slightly more actively bacteriostatic on a weight basis. The reverse appears to be true of bactericidal effect. Gourevitch and his colleagues (1958), using serial transfer techniques on *Staphylococcus aureus* and *Escherichia coli*, have demonstrated the development of resistance to kanamycin *in vitro* in a slow, stepwise fashion. Resistance of mycobacteria develops at a more rapid rate.

ABSORPTION, DISTRIBUTION, AND EXCRETION

Kanamycin is absorbed rapidly when injected intramuscularly, peak concentrations being reached within one hour (Welch *et al.*, 1958). The levels fall rapidly in six hours and little drug can be detected in the serum twelve hours after a single injection. The levels attained in the serum are approximately the same as those following an equivalent dose of streptomycin or dihydrostreptomycin. Most of the antibiotic is excreted in the urine within twenty-four hours after it is administered, approximately 80 per cent. being excreted in the first six hours after medication. There is no accumulation of kanamycin in the serum when given at 12-hour intervals in patients with normal renal function. There is little serum binding of the antibiotic, and it is excreted exclusively by glomerular filtration following parenteral administration. It is distributed in highly vascular organs, such as the liver and kidney, and appears in concentrations approximately equivalent to the blood level. Penetration into the spinal fluid, bone and heart muscle is poor (Tisch *et al.*, 1958).

There has been little experience with intravenous administration, since it is absorbed so rapidly following intramuscular injection. Apparently it is tolerated well when administered intravenously, in that thrombophlebitis does not seem to be a problem. Kanamycin is so poorly absorbed following oral administration that blood levels are extremely low or not detectable.

CLINICAL USES

Kanamycin has been used in the treatment of a wide variety of bacterial infections and the clinical results have generally paralleled the *in vitro* studies (Finland *et al.*, 1958; Yow and Monzon, 1958; Yow and Womack, 1958; Bunn *et al.*, 1958). Most acute infections due to such kanamycin-sensitive organisms as *Staphylococcus aureus*, *E. coli*, *Mycobacterium tuberculosis*, *B. anthracis*, and the *Aerobacter-klebsiella* group have responded promptly to the administration of kanamycin. Infections due to sensitive strains of *Proteus* and *Pseudomonas* have likewise improved. Infections due to species generally resistant, such as *Diplococcus pneumoniæ*, most streptococcal species and most anaerobic organisms, or resistant strains of proteus, pseudomonas, and the aerobacter-klebsiella group have not been favourably

influenced by kanamycin therapy. Some very striking exceptions occur in this *in vitro-in vivo* relationship; brucella and salmonella for example, are quite sensitive *in vitro* to kanamycin, but patients with brucellosis and typhoid fever treated with kanamycin have not usually responded clinically (Sanchez and Sanchez, 1958). The course of some other salmonella infections and of most shigella infections treated so far has been altered favourably by kanamycin therapy (Thurman and Platou, 1958).

The use of kanamycin in the treatment of various forms of tuberculosis has been most extensive in patients failing to respond to established forms of therapy, but results have generally been quite encouraging (Donomae *et al.*, 1958). Its activity appears to be about equal to that of streptomycin. The acoustic nerve injury associated with the prolonged administration of kanamycin will probably limit the dosage to 3 grammes weekly when it is to be used over a long period.

The effect of the oral administration of kanamycin on the bacterial flora of the intestinal tract appears to be identical to that of neomycin; that is, the coliform bacteria, proteus, pseudomonas, and klebsiella are usually rapidly eliminated, but the fæcal streptococci, monilia, bacterioides and the clostridii usually persist. This suppressive effect of kanamycin and neomycin on the bacterial flora of the bowels is presumably the explanation for the lowering of the blood ammonia associated with the administration of either in patients with liver failure. Some patients required doses as large as 8 to 12 grammes daily to produce a reduction and in some the effect is not sustained or reproducible.

Kanamycin has been used locally in the treatment of superficial infections and as a supplement to its systemic administration. Ointments containing 0.5 to 3 mg./ml. produce an effect similar to that associated with the use of neomycin in superficial pyodermas. Because of the difficulties associated with the sterilization of walled-off infections and infections in body cavities with systemically administered antibiotics, kanamycin has been instilled locally in abscess cavities, draining sinuses, the peritoneal cavity, pleural spaces and subarachnoid space. The concentration injected into the subarachnoid space has been 0.5 mg./ml., and the largest daily dose has been 5 mg. Concentrations varying from 2.5 mg./ml. to 50 mg./ml. have been used in other sites, with a maximum daily dose of 1 g. Since at least part of the antibiotic instilled locally is absorbed, the amount administered in this fashion must be taken into consideration in calculating the total daily dose to be given to the patient.

USE IN STAPHYLOCOCCAL INFECTIONS

Even though there are quantitative variations in the sensitivity of staphylococci to kanamycin *in vitro*, depending upon the method used, all strains studied thus far appear to be inhibited *in vivo* when the presently recommended dosages are used and if the antibiotic actually comes into contact

with the bacteria. The single exception to this occurs in some instances of so-called 'overwhelming infections' such as is seen in acute staphylococcal endocarditis. Examples of the beneficial and sometimes life-saving effect of kanamycin in the treatment of many staphylococcal infections have now been reported. These include such conditions as pneumonia, lung abscesses, acute sinusitis, otitis media, meningitis, brain abscesses, acute endocarditis, acute osteomyelitis, pyelonephritis, wound infections, furunculosis, suppurative thrombophlebitis, empyema, prostatic abscesses, and infected gangrene. Most of the patients treated have already failed to respond to one or more other antibiotics and many of them have had other serious systemic diseases.

ADMINISTRATION AND DOSAGE

Kanamycin is usually administered by the intramuscular route in systemic infections. The currently recommended daily dose in adults is 1.0 to 1.5 g. and in children 15 mg./kg., given in divided doses every six to twelve hours. In severe infections this dose may be doubled for short periods of time.

The drug is not sufficiently absorbed when administered by the oral route to produce therapeutic levels, but this method of administration has been used as a means of preparing the patient for bowel surgery, for treating ammonia intoxication due to liver failure, and it might well be used for the treatment of such enteric infections as staphylococcal enterocolitis. It has been administered intravenously in a few cases, but this route offers little advantage since the antibiotic is absorbed so rapidly when injected intramuscularly. Kanamycin can be administered locally and concentrations of 2.5 mg./ml. have not appeared to be irritating to serous or mucous membranes. Concentrations of 5 mg./ml. or higher have been instilled into abscess cavities without pain or other evidence of irritation.

TOXICITY

The greatest hazard of kanamycin therapy is that of injury to the acoustic nerve. This is similar to that seen in association with the administration of dihydrostreptomycin and neomycin. Animal toxicity studies indicate that this is related to the magnitude of the daily dose and the total amount administered. It has been difficult to appraise accurately the details of the toxic effect of kanamycin on the 8th cranial nerve because of the seriousness of the illness of most of the patients receiving kanamycin and the variations in the dosage schedules in the early months of its clinical trials, but the most careful studies have been performed by Finegold *et al.* (1958). The findings of this group indicate that if frequent audiograms are performed, perceptive hearing loss of 40 decibels or less can be demonstrated not infrequently in patients receiving more than 40 mg./kg./day for periods exceeding two weeks. Of 11 patients receiving doses of from 40 to 60 mg./kg./day for six to twenty-eight days, nine showed audiographic changes

and three of the nine had losses in the conversational range. Three of the 11 also had evidence of vestibular damage. Five of these patients had pre-existing renal damage. In patients receiving smaller daily doses, much milder and often transient auditory damage was evident, and much longer periods of therapy were required to produce audiographic changes. In most instances the hearing loss begins in the high frequency ranges and is preceded by tinnitus. If the antibiotic is discontinued during the time that tinnitus is prominent, withdrawal of the drug results in a reversal of the hearing loss. If kanamycin is continued permanent loss progresses so long as the drug is given, but not after it is discontinued.

Observations by several investigators suggest that children tolerate larger amounts of kanamycin. One 6-year-old child, for example, received doses of from 30 to 60 mg./kg./day for forty days without audiographic evidence of hearing loss and another received between 35 and 50 mg./kg./day for ninety days.

A factor of considerable importance in regard to auditory toxicity appears to be the rate at which the antibiotic is excreted. Since kanamycin is excreted almost exclusively by glomerular filtration, disorders associated with a decreased glomerular filtration are likely also to be associated with increased blood levels of kanamycin and consequent increased toxicity. This is most apt to be observed in diabetic patients with insufficiently severe Kimmelstiel-Wilson's disease. Hearing loss has been reported to occur as early as one week after beginning therapy in patients with marked renal insufficiency.

Another problem of concern regarding the toxicity of kanamycin is that of renal injury. The experience with the use of the closely related antibiotic, neomycin, and the results of animal toxicity experiments with kanamycin strongly suggest that this would be a problem in the clinical use of the antibiotic. Whilst many patients receiving kanamycin exhibit evidence of mild renal irritation as manifested by cylinduria and occasionally albuminuria and microscopic hæmaturia, the only clear-cut evidence of serious renal toxicity is that of sudden oliguria occurring in a patient reported by Berman and Katz (1958). This patient recovered when the drug was withdrawn. Renal clearance studies on patients receiving kanamycin revealed mild changes in one function or another in most patients. The significance of these changes has not been fully evaluated, but serious renal toxicity cannot be a frequent problem when one considers the fact that so few patients with preceding moderate to severe degrees of renal failure have shown evidence of aggravation of their disease with relatively large doses of kanamycin. Most patients with serious systemic diseases and often marked fluid and electrolyte disturbances, have been treated with quite large doses of kanamycin and none has developed more than transient increases in urine retention that could be attributable to the antibiotic.

Skin rashes of the maculo-papular type have occurred in association with

kanamycin, but in most instances they have been so mild that it has not been necessary to stop the drug. Eosinophilia has been noted with some frequency, but is apparently of no clinical importance. No other changes in the hæmopoietic system, liver function, or electrocardiogram have been described.

CONCLUSIONS

Kanamycin appears to be one of the most effective anti-staphylococcal antibiotics available today. It is also active against most strains of *E. coli*, *Proteus sp.*, the *Klebsiella pneumoniæ-Aerobacter aerogenes* group, and many strains of *Pseudomonas aeruginosa* resistant to other antibiotics. It is usually ineffective in the treatment of infections due to *Diplococcus pneumoniæ*, *Streptococcus sp.* and the anaerobic bacteria. It is bactericidal in its effect and is absorbed rapidly following intramuscular administration. It has the disadvantage of producing acoustic nerve injury when it is administered for long periods of time, or extremely high blood levels are maintained for short periods of time. Nephrotoxicity has not been a frequent serious complication, but it is a potential hazard.

Kanamycin has been administered successfully in virtually every known staphylococcal infection. In many instances its effect has been dramatic and life saving, but when the causative organism occurs in avascular areas, systemic administration will not usually eradicate the staphylococci and surgical therapy must be used as a supplement to antibiotic therapy.

Because of the toxicity associated with intense or prolonged use of kanamycin it should not be used in mild or self-limited infections or in patients with renal insufficiency, but it should not be withheld in moderately severe or severe infections.

References

Berman, L. B., and Katz, S. (1958): *Ann. N.Y. Acad. Sci.*, **76**, 149.
Bunn, P. A., Baltch, A., and Kranjnyak, O. (1958): *Ibid.*, **76**, 109.
Cron, M. J., *et al.* (1958): *Ibid.*, **76**, 27.
Donomae, I., *et al.* (1958): *Ibid.*, **76**, 166.
Finegold, S. M., Winfield, M. E., Aronsohn, R. B., Hewitt, W. L., and Guze, L. B. (1958): *Ibid.*, **76**, 319.
Finland, M., *et al.* (1958): *Ibid.*, **77**, 17.
Gourevitch, A., Rossomano, V. Z., Puglisi, T. A., Tynda, J. M., and Lein, J. (1958): *Ibid.*, **76**, 34.
Sanchez, F. Ruiz, and Sanchez, A. Ruiz (1958): *Ibid.*, **76**, 235.
Thurman, W. G., and Platou, R. V. (1958): *Ibid.*, **76**, 230.
Tisch, D. E., Huftalen, J. B., and Dickinson, H. L. (1958): *Ibid.*, **76**, 44.
Umezawa, H., *et al.* (1957): *J. Antibiot.*, Ser. A, **10**, 181.
Welch, H., Wright, W. W., Weinstein, H. I., and Staffa, A. W. (1958): *Ann. N.Y. Acad. Sci.*, **76**, 66.
Yow, E. M., and Monzon, O. T. (1958): *Ibid.*, **76**, 372.
Yow, M. D., and Womack, G. K. (1958): *Ibid.*, **76**, 363.

PRACTICAL DIETETICS

VI.—SLIMMING DIETS

By M. E. CAREY, B.Sc.

Chief Dietitian, St. George's Hospital

ANY diet which supplies fewer calories in a day than the amount of calories used in a day will reduce weight, provided that fluid is not being retained. Consequently many slimming diets have been in fashion from time to time. These diets may be based on such items as orange juice, yoghourt, milk, bananas, fatty foods or non-fatty foods, or indeed any other food or combination of foods. The common factor in such varied diets is that, in the amounts of food actually consumed, calories supplied fall short of the day's requirement, and the balance is supplied from body tissue, usually fat.

MAINTAINING GOOD NUTRITION

For a day or two, almost any diet low enough in calories could be used for slimming, novelty outweighing considerations of palatability and ease of dieting. If a slimming diet is medically necessary, it implies that weight reduction is to be considered in terms of several pounds, or even stones, and consequently that the diet must be continued for more than a matter of days. This immediately raises the question of good nutrition on a low calorie intake: the diet must still supply adequate protein, minerals and vitamins, and some carbohydrate and fat. Of these nutrients, protein and carbohydrate each supply approximately 4 calories per g., and fat 9 calories per g. The problem of which calorie foods to cut out is complicated by the fact that the vast majority of foods supply more than one nutrient, and the low-calorie diet must still be nutritionally sound. The problem is comparable with that of packing all the essentials for a holiday into one small suitcase instead of a large one.

Theoretically, the first food to cut out would be one which supplies calories in the diet, and nothing else. Sugar is in this category, and is the first food to ban on a slimming diet, together with glucose and honey, despite the view of some followers of fashionable diets, that in some magical way these foods give energy without the possibility of putting on weight. Saccharin or 'saxin' may be used to sweeten foods without adding any calories to the diet. From this point there are many ways of theoretically constructing a nutritionally adequate low-calorie diet: that is, one supplying sufficient protein, minerals and vitamins, and some carbohydrate and fat. In practice, the scope is limited by cost, palatability, and consumer reaction. No slimming diet can slim unless it is eaten to the exclusion of other foods. There is a popular fallacy that some foods are slimming in the sense that eating them will actually take off weight. It is not unknown for a person on a

diet to eat a slimming diet and other foods in addition, in the belief that the diet will still take off weight.

COST AND PALATABILITY

A low-calorie diet is bound to cost more than a normal diet, as cheap calorie foods, such as sugar, bread, potatoes, and fats, must be limited to some extent, and the amount of fruits and vegetables in the diet proportionately increased. If the diet is stated in general terms, it leaves scope for a wide cost range: from 'slightly more expensive' to 'much more expensive'. Lean meat could be interpreted as lean stewing steak, or chicken, and green vegetables as cabbage or asparagus.

Palatability is a matter of individual choice. Food habits are far more than a means of satisfying hunger; they are an integral part of our lives, and a diet is more likely to be followed if it is stated in terms of familiar, easily obtainable foods.

EATING AT HOME AND 'EATING OUT'

Another problem is that most people have some of their meals as part of a family group. There may occasionally be a family where all need to lose weight, but this is the exception. In general, a diet must be adaptable to the meal habits and food choice of the rest of the family, involving the minimum of change in the menu. For example, if the family are having steak pie, cabbage, potatoes, and baked apple with syrup and raisins, for a meal, the overweight member of the family could eat lean steak (without the pastry), cabbage, a small quantity of potatoes (or replace potato by another vegetable), and have his baked apple cooked without syrup or raisins, and subsequently sweetened with 'saxin' or saccharin.

Eating out becomes a problem of eating round high-calorie foods and choosing low-calorie foods.

THAT 'SINKING FEELING'

Low-calorie diets can easily give a feeling of hunger, especially in people accustomed to eating high-calorie snacks between meals. This can be largely overcome by including plenty of fruit and vegetables in the diet to give bulk, and by spacing meals and snacks out evenly over the day. A person used to eating, say, two main meals a day may be better advised to try to re-arrange his meal pattern when going on a slimming diet.

Fat has a satiety value in the diet: it helps to prevent that 'sinking feeling' by delaying gastric emptying, but weight for weight, supplies over twice as many calories as protein or carbohydrate foods, and usually in a far more concentrated form, as less water is associated with fatty foods. For example, 1 ounce (28 g.) of butter (14 per cent. water) supplies over 200 calories, whereas 1 ounce (28 g.) of lean meat (50 per cent. water) supplies approximately 70 calories, and 1 ounce (28 g.) of vegetable marrow (98 per cent. water) only 2 calories.

SIMPLICITY AND EXPLANATION

A diet must be easily understood, preferably with the minimum of mathematics. Some people like to count calories for each meal, but the majority prefer to eat without mental calculations. A slimming diet stated in general terms, cutting out some foods altogether, limiting the amounts of others, and allowing a free choice of the rest, is easy to follow, and reduces weight

	DIET I (800 CALORIES)	DIET II (1000 CALORIES)
Breakfast:	Skim milk from allowance, in tea or coffee 1 thin slice of bread Butter from allowance Egg, lean bacon, haddock or kipper Grapefruit if desired	Milk from allowance in tea or coffee 2 thin slices of bread Butter from allowance Egg, lean bacon, haddock or kipper Grapefruit if desired
Mid-morning:	Tea or coffee, with milk from allowance, or Bovril, Oxo, or Marmite	Tea or coffee, with milk from allowance, or Bovril, Oxo, or Marmite
Lunch:	Lean meat, fish, cheese or eggs Green vegetables or salad Root vegetables, e.g. carrot, onion or turnip Fruit, fresh or stewed, without sugar	Lean meat, fish, cheese or eggs Green vegetables or salad Root vegetables, e.g. carrot, onion or turnip Fruit, fresh or stewed, without sugar
Tea:	1 thin slice of bread Butter from allowance Tea, with milk, from allowance Salad, Marmite, tomato or paste	1 thin slice of bread Butter from allowance Tea, with milk from allowance Salad, Marmite, tomato or paste
Supper:	Lean meat, fish, cheese or eggs Green vegetables or salad Fruit, fresh or stewed, without sugar 1 thin slice of bread Remainder of skim milk in tea or coffee	Lean meat, fish, cheese or eggs Green vegetables or salad Fruit, fresh or stewed, without sugar 1 thin slice of bread Remainder of milk in tea or coffee
Daily:	½ pint (285 ml.) skim milk ¼ ounce (7 g.) butter	½ pint (285 ml.) milk ½ ounce (14 g.) butter

satisfactorily. A 1000-calorie diet on these lines does not supply exactly a thousand calories each day, but over a period of days will supply approximately a thousand calories a day on average. It is important to discuss a slimming diet with the individual, to sort out problems, and to follow up to check that weight loss is at a satisfactory rate. Some people may cut down on a given diet in an attempt to lose weight faster; others may unwittingly take extra calories as a result of advice from friends and relatives.

SOME COMMON ERRORS

Some common errors are that diabetic foods made with sorbitol are 'all right' as they do not contain sugar, and that diabetic chocolate is 'slimming'. A wealth of myth information exists on the subject of breads. It is not

always realized that brown or white bread has approximately the same calorie value; that some 'starch-reduced' breads are so very slightly starch reduced that, in the quantities eaten, the calorie value differs very little from ordinary bread; and that the calorie value of a slice of bread is still the same, whether that bread is made with or without salt, eaten as bread, or made into toast. Friends often advise people on a diet to cut down on salt or on

	DIET III (1,200 CALORIES)	DIET IV (1,500 CALORIES)
Breakfast:	Milk from allowance, in tea or coffee 2 thin slices of bread Butter from allowance Egg, lean bacon, haddock or kipper Grapefruit if desired	Milk from allowance, in tea or coffee and on cereal Medium serving cornflakes (½ ounce (14 g.)) 2 thin slices of bread Butter from allowance Egg, lean bacon, haddock or kipper Grapefruit if desired
Mid-morning:	Tea or coffee with milk from allowance	Tea or coffee with milk from allowance 2 plain biscuits
Lunch:	Lean meat, fish, cheese or eggs Green vegetables or salad 1 medium potato or 1 thin slice of bread Root vegetables, e.g. carrot, onion or turnip Fruit, fresh or stewed, without sugar	Lean meat, fish, cheese or eggs Green vegetables or salad 1 medium potato or 1 thin slice of bread Root vegetables, e.g. carrot, onion or turnip Fruit, fresh or stewed, without sugar
Tea:	2 thin slices of bread Butter from allowance Tea, with milk from allowance Salad, Marmite, tomato or paste	2 thin slices of bread Butter from allowance Tea, with milk from allowance Salad, Marmite, tomato or paste
Supper:	Lean meat, fish, cheese or eggs Green vegetables or salad 1 medium potato or 1 thin slice of bread Fruit, fresh or stewed, without sugar Remainder of milk in tea or coffee	Lean meat, fish, cheese or eggs Green vegetables or salad 1 medium potato or 1 thin slice of bread Fruit, fresh or stewed, without sugar Remainder of milk 2 plain biscuits
Daily:	½ pint (285 ml.) milk ½ ounce (14 g.) butter	¾ pint (428 ml.) milk ¾ ounce (21 g.) butter

fluids, confusing fat loss with fluid loss. On a normal slimming diet, the number of cups of tea would be immaterial, but the amount of milk used, and the presence or absence of sugar, would affect the weight loss.

DIETS

The diets shown in this article have been used for hospital outpatients. Encouragement, and incentive to diet, work in conjunction with the diet sheet to reduce weight. Inability to get into a favourite suit has often acted as a spur to continued dieting.

FOODS NOT ALLOWED IN SLIMMING DIETS

Sugar, glucose, sweets, chocolate, jam, marmalade, syrup, honey, and other preserves.
Breakfast cereals*, rice, porridge, macaroni, spaghetti.
Milk puddings, custard, ice-cream.
Cakes, biscuits*, pastry, steamed and suet puddings.
Sweetened tinned milk, evaporated milk.
Dried fruit, crystallized fruit, nuts, coconut.
Grapes, bananas, tinned fruit.
Peas, haricot beans, lentils, beetroot.
Potatoes*.
Fried foods, greasy or fatty foods, sausages.
Beer, wines and spirits.
Sweetened fruit squash, ginger ale, cider.
Mineral waters, except soda water.
(Foods marked * are allowed on some of the diets, but only in the amounts stated).

The series of slimming diets, 800, 1000, 1,200 and 1,500 calories, should produce a satisfactory rate of weight loss in most obese persons. If a less strict diet is required, it is usually sufficient to cut out sugar and alcohol entirely, and to limit the amount of fried and fatty foods in the diet.

Food Exchanges.—Butter and margarine are interchangeable on these diets. One thin slice of bread may be replaced by one medium potato (3 ounces [85 g.]) or by two Ryvitas or two cream crackers.

REVISION CORNER

THE ANÆSTHETIST'S BAG

THE general practitioner anæsthetist will not require as much apparatus as his consultant colleague; yet there is a certain basic minimum which he should carry for the safety of the patient, and which will enable him to deal adequately with any emergency which might arise.

APPARATUS

A Boyle's or similar machine is almost a *sine qua non*, but 'rotameters', though preferable, are not absolutely essential. All that is required is a set of reasonably accurate flowmeters for nitrous oxide, oxygen and possibly carbon dioxide. Cylinders of 100 gallons (455 litres) of nitrous oxide, and of 30 gallons (135 litres) of oxygen, fitted with reducing valves, will be needed, and it is well to carry some CO_2 as 'J' size sparklet bulbs.

Two adult facepieces, medium and large, are needed, together with a child's size; airways such as Phillips' or Guedel's, sizes two and three, will also be necessary. Two throat sprays, one metal for spraying the larynx, and one glass for the pharynx, should find a place in the bag and some form of lubricant such as 'K-Y' jelly or lignocaine ointment or jelly.

Endotracheal apparatus should always be carried, and a Macintosh laryngoscope with large and small blades will be found satisfactory, but do

not forget a spare battery and spare bulbs. Magill oral endotracheal catheters sizes 2 to 9, and size 4 to 7 nasal, should be all that are needed, but Magill forceps and a malleable introducer should be included. A set of Magill's nasal connectors and Cobb's oral connectors will be found advisable, but this is a personal choice. One or two Woodfield Davis flanged nasopharyngeal tubes are invaluable when anæsthetizing the difficult patient whose respiration is obstructed and whose jaw is tightly clenched.

Intravenous apparatus is required both for induction and possible resuscitation. For this purpose sterile syringes of 2, 5, 10, and 20 ml. capacity are required, whilst for resuscitation it is well to carry an intravenous infusion set ready sterilized with an adequate length of latex rubber tubing. Suitable needles will be required both for filling and for venepuncture; for this latter purpose an 'evipan' or no. 18 needle will be found suitable, whilst a Mitchell or Gordh needle may be carried in case an indwelling needle is required. For intravenous infusion, either the West Middlesex Hospital cannula or the author's needle cannula is recommended, together with a small bladed scalpel, fine dissecting forceps, small sharp pointed scissors, and mosquito forceps which may be needed if it is found necessary to cut down on a vein. Finally, a bottle of sterile 4.3 per cent. glucose in 0.18 per cent. saline should be available.

DRUGS

For induction.—Thiopentone, both 0.5 gramme and 1 gramme ampoules, is needed together with an adequate supply of the relaxants, suxamethonium, gallamine triethiodide and tubocurarine chloride. Pethidine, 50 mg. ampoules, should be included with, perhaps, some 'pethilorphan' as a refinement. The latter contains 100 mg. of pethidine with 2.5 mg. of levallorphan to counteract the respiratory depressant effect of pethidine.

For restoration of respiratory function.—Ampoules of 1/100 grain (0.6 mg.) of atropine sulphate, which is injected intravenously before neostigmine is given, should always be at hand. Neostigmine is put up in two strengths: a clear glass ampoule containing 0.5 mg. and an amber one which contains 2.5 mg. This may be required for the reversal of curarization. Nikethamide, in 5-ml. ampoules, is very useful for stimulating respiration in cases of barbiturate overdose, and I have also found this drug most useful in counteracting bronchospasm following the use of thiopentone. Aminophylline may also be used for this purpose.

Pressor drugs may be extremely useful on occasion and I would recommend that ampoules of 1 in 1000 adrenaline, noradrenaline, methoxamine and methylamphetamine should be carried. Horton and Davison recommend the use of ouabain, 0.25 mg. intravenously, in the treatment of shock.

The cardiovascular emergency calls for prompt and courageous treatment, and cardiac massage should be started quickly. I have, however, seen prompt recovery after the injection of 1 in 1000 adrenaline through the fourth intercostal space into the ventricle, but it must be remembered that

delay in starting cardiac massage will rapidly prove fatal. It is wise to carry a no. 1 hypodermic needle ready sterilized, together with a 10-ml. syringe, so that an ampoule containing 1 ml. of 1 in 1000 adrenaline may be diluted with 9 ml. of normal saline to form a solution of 1 in 10,000 adrenaline for injection into the heart by direct vision. There should also be at hand an ampoule of 10 ml. of 1 per cent. calcium chloride for the same purpose. It is a good plan to keep the cardiac emergency syringe and drugs in a small box ready labelled.

MISCELLANEOUS REQUIREMENTS

It is a wise man who carries a tracheostomy set, although I have only needed to do an emergency tracheostomy on one occasion in private practice. Nevertheless, this was a life-saving measure. Perhaps I may be forgiven for recommending that the older methods still have a place, and would suggest that a Bellamy Gardner ether mask and dripper may prove useful, and that a Mills chloroform drop bottle may also have a place. Finally, the bag should contain a bottle of diethyl ether, trichloroethylene, perhaps chloroform and certainly some ethyl chloride.

FRANKIS T. EVANS, M.B., B.S., F.F.A.R.C.S.
Anæsthetist, and Lecturer in Anæsthetics, St. Bartholomew's Hospital.

STITCH IN THE SIDE

THE original meaning of 'stitch' was a stab inflicted by a pointed instrument; and later, a sudden local pain like that produced by the thrust of such a weapon. 'Stitch in the side' is nowadays popularly associated with exercise. The same sort of pain, however, may result from jolting the body as in riding a camel, a horse with a jerky action, or a motor-cycle on a rough road. It may even occur when in a motor-car indifferently sprung or upholstered.

The exercise *par excellence* to produce a stitch is running or fast walking, for the erect, or nearly erect attitude is almost a *sine qua non*. Swimmers very rarely suffer, and oarsmen never. When the sufferer from stitch lies on his back, the pain usually disappears and does not recur from exercise when in this position: e.g. supporting the hips in the air, and swinging the legs.

The commonest situation of the pain is the upper abdomen, the right side more often than the left. More rarely the site is the lower abdomen, the epigastrium, or thorax. Pain in the shoulder is occasionally associated with abdominal pain on the same side. The site of pain is not constant in the same person on different occasions.

Stitch is more likely if exercise is undertaken after eating or drinking; the more taken and the shorter the interval before exercise, the more severe the stitch.

CAUSATION

Incrimination of the spleen, as in Biblical and classical references, persisted until comparatively recently. It was supposed that the pain resulted from

stretching of its capsule through congestion. Such an explanation would not account for right-sided pain (save in the subjects of transposition of viscera); and, by marsupializing the spleen, Sir Joseph Barcroft showed that it contracted during exercise. Ischæmia of the diaphragm has been advanced as the cause, analogous to other ischæmic (painful) occurrences such as angina pectoris and intermittent claudication. There are, however, cogent objections to this explanation even in the case of exercise, still more when jolting movements are responsible.

Stitch is almost certainly due to strain on the peritoneal ligaments attached to the diaphragm. In the erect attitude, the heavy viscera—stomach, liver and spleen—are partly supported by the abdominal wall, and, if for any reason this is unable to provide adequate support, stretching of these ligaments is intensified. With the hyperpnœa of exercise, at one phase during each gasping breath there is complete relaxation of the muscles maintaining intra-abdominal pressure. If a violent movement or jolt coincides with this relaxation, the result must be an intermittent tug at the attachment of the ligaments to the diaphragm and reference from the peritoneal lining to various situations according to nerve supply. (Tension is the adequate stimulus to irritate the sensitive peritoneal nerve endings.) Any additional load in the stomach will be a contributing factor.

TREATMENT

Relief is sometimes attained by bending the body to the affected side and by pressure of the hand to limit diaphragmatic movement. In this way the runner may experience a 'second wind' so to speak, because his breathing becomes more shallow and better coordinated. Tight corsets are of service as abdominal supporters, but any such arrangement is clearly inapplicable during athletic performance although of use to riders and others in whom jolting is the provocative factor. An obvious elementary precaution is to refrain from eating or drinking within, say, three hours of a run.

But there are remarkable individual variations. Some athletes, despite a large indigestible meal even less than two hours before exertion, perform without the slightest discomfort: others suffer from stitch after the tiniest indulgence. It seems that there must be a constitutional susceptibility to stitch in some subjects, although on what this depends can be only hypothetical. The explanation may be anatomical, or on the lines of threshold of consciousness as in the familiar medical problem related to visceroptosis which as such does not cause symptoms but demands the accompaniment of some other element. Some athletic authorities believe that precautions against cold assist in prevention, especially protection of the knees and wrists which appear to be especially vulnerable. Such a precaution is at least harmless.

SIR ADOLPHE ABRAHAMS, O.B.E., M.D., F.R.C.P.
Consulting Physician, Westminster Hospital; Honorary Medical Adviser, International Athletic Board.

NOTES AND QUERIES

A Spanish Holiday

QUERY.—My wife and I and our two girls of 3 and 2 years are going to occupy a villa on the Costa Brava in June and July this year, for our holiday. Could you advise me on the dangers of the Spanish food and drink, what precautions to take and what drugs to include in an emergency pack?

REPLY.—First and foremost it is essential to be inoculated against typhoid and paratyphoid fevers. It is wise to do this in fact even for a holiday in France, for typhoid can be acquired quite readily anywhere from Normandy to the Mediterranean. At the same time it would be a pity to omit the opportunity of being inoculated against tetanus, in view of the various accident hazards involved in travelling and especially if travelling by car.

The common complaint in hot weather is gastroenteritis which is associated with food infection spread by flies, dirt and so forth. Sulphaguanadine is probably the drug of choice and nearly always brings the attacks of diarrhœa to a stop within a day or two, although a Sonne dysentery may be more persistent. An excellent preparation with a wider field of action, and one which is palatable and therefore taken readily by children, is 'Ivax' (Boots) containing sulphaguanadine 4 g., kaolin 6 g., and neomycin sulphate 300 mg., in each fluid ounce (28.5 ml.). This might be taken as a useful standby in case sulphaguanadine alone fails. There are no special dangers of Spanish food; it is largely a matter of how it is cooked, above all things in relation to cleanliness, but the fondness for cooking in oil often upsets English visitors, giving rise to nausea and some looseness of the bowels. Spanish drink, apart from water, has no greater dangers than drinks in any other country.

A. H. DOUTHWAITE, M.D., F.R.C.P.

When to Start Mixed Feeding

QUERY (from a reader in Northern Ireland).—What are the advantages, if any, of starting mixed feeding of infants at the age of six weeks? In some hospital clinics this is advised. At nine or ten weeks the recommended daily diet includes 2 ounces (by weight) of cereal, an egg, and 'a rasher of bacon crisply fried, pounded, and added to the cereal'.

REPLY.—There are no important advantages in starting mixed feeding at the age of six weeks. Milk is a well-balanced food which nourishes babies quite satisfactorily in the early months provided they are allowed to take as much as desired and are not fed according to the book. This is important as some babies require and therefore take twice as much as the average baby, just as some adults require and take twice as much as others who are doing the same work. The only advantage of starting mixed feeding early is to prevent a slight fall in the hæmoglobin level caused by the low iron content of cow's milk, but this is not important as the slight hypochromic anæmia is soon rectified when mixed feeding is started at the age of three to four months—the age usually recommended in this country. Starch-splitting enzymes are much more plentiful in the digestive secretions after the first few months, showing that nature has not provided for the introduction of mixed feeding at a very early age.

It is arguable that very young infants usually thrive well with additional mixed feeding. This is true, but a small proportion show signs of indigestion such as meteorism and fretfulness. Why therefore run such an unnecessary risk? Fashion, and the intensive barrage of advertisements by manufacturers of baby foods in favour of the early introduction of mixed feeding, are the principal reasons for this continuing unphysiological trend.

The first addition to the milk diet at three to four months should be sieved vegetables in gradually increasing amount to supply additional iron. Next, cereal should be introduced at four months with cow's milk feeding and at six months with breast milk feeding. In all, egg, minced red meat or liver, potatoes and fruit should gradually be introduced between six and eight months. It is unusual to give bacon, even at this stage, in Britain, but why not a little tasty Irish bacon if baby likes it!

PROFESSOR J. L. HENDERSON, M.D., F.R.C.P.

Intractable Auricular Fibrillation

QUERY.—A woman, aged 62, with known hypertension of several years' duration (blood pressure 220/110 mm. Hg) was seen as an emergency with pulmonary œdema and auricular fibrillation. There was some improvement initially with a low-salt diet, mersalyl injections twice weekly, and digitalis. The improvement was not maintained for more than a few weeks and it proved impossible to reduce the apex rate below 140, although the digitalis dosage was increased to the point of toxicity. (The patient was seen a few weeks before death by a local consultant who agreed with the diagnosis of myocardial degeneration and auricular fibrillation). I would be glad of an expert view on the etiology and management of a case of fibrillation not responding to digitalis.

REPLY.—When auricular fibrillation with a rapid ventricular rate does not slow with digitalis there is usually a good reason. In the patient quoted the reason was probably gross ischæmic heart disease complicating hypertension, and the persistently high rate carried the usual bad prognosis. Anti-thyroid treatment with carbimazole offers some hope of improvement. The suggested dose is 10 mg. twice daily for ten days, 5 mg. thrice daily for a week, then 5 mg. daily indefinitely. Cryptic thyrotoxicosis uræmia, pulmonary infarction, sepsis (e.g. a silent pelvic abscess), chronic alcoholism, chronic emotional stress, ephedrine or isoprenaline for bronchial spasm, and in younger persons relapse of rheumatic carditis, may occasionally be responsible for total or partial failure of the ventricular rate to respond to digitalis. A persistently rapid ventricular rate may be simply a sign of cardiac defeat.

It is remarkable, however, that despite those conditions, digitalis can, and often does, slow the ventricular rate satisfactorily and one's respect for its potency is not shaken by its occasional failure.

C. J. GAVEY, M.D., F.R.C.P.

Leucotomy in Affective States

QUERY.—I should be much obliged if you could refer me to suitable literature dealing with the modified leucotomy operation, especially with regard to involutional melancholia, mortality, and subsequent personality effects. The patient under consideration is over 60 years of age.

REPLY.—A very fair review of the operations available and their indications is to be found in chapter IX of Sargant and Slater's 'Physical Methods of Treatment in Psychiatry' (Livingstone, 1954). A general account is also given in Sargant's 'Ten Years' Clinical Experience of Modified Leucotomy Operations' (*Brit. med. J.*, 1953, **ii**, 800). Since then new modifications such as cingulectomy have not shown any advantage over the infero-medial quadrant operation for cases of involutional melancholia. A recent trend is to deal with this area by electrocoagulation with an accurate stereotactic technique, the approach being made through burr-holes at the vertex. These more limited operations, whilst having the advantage of minimal trauma and personality change, may not always achieve enough change in the depression at the first attempt, so that the inferior quadrant operation is still the most generally useful. It must be remembered that patients referred for leucotomy because of failure of electroconvulsive therapy not infrequently recover and remain well if given another course, having by then reached a more favourable stage of the depressive illness.

A recent survey by Robin (*J. ment. Sci.*, 1958, **104**, 1025) gives a rather unfavourable impression of the results of leucotomy in affective states. Although the physical dangers are somewhat increased, good results are often obtained in elderly depressives whose illness threatens to become chronic. Serious personality changes are not common unless an underlying dementia has been missed or local hæmorrhage increases the extent of the operation. It is not possible to give the operative mortality by age for the modified leucotomies, the extent of which differ with each surgeon, but even at the age of 60 it is probably well below 2 per cent. With stereotactic coagulation the risks are less but the therapeutic effects will be less predictable until more experience has been gained.

PROFESSOR ALEXANDER KENNEDY, M.D., F.R.C.P., D.P.M.

Cæsarean Section

QUERY (from a reader in Belgium).—On account of a malformation of the sacrum a patient is unable to have children except by Cæsarean section. Is it not a fact that Cæsarean sections should not be repeated too frequently? This patient has had two children. What is the best method of pregnancy prevention: fallopian tube ligature, male tube ligature, contraceptives? In the case of the latter what are the best methods available? Is any danger involved?

REPLY.—Opinions vary as to the number of Cæsarean sections permitted. Some obstetricians suggest sterilization after three, some after five. The decision would be influenced by the age and general condition of the woman, the number of children she desired, and by religious principles which might be involved. Because of the irrevocable nature of the operation, sterilization of the female or of the male is undertaken as a last resort, and contraceptive methods may therefore be preferred. The use of the occlusive cap by the female, or the sheath by the male, are the most reliable methods of contraception, provided that these are used in conjunction with a spermicidal preparation. The sheath method is simpler as it does not involve the careful fitting, instruction, and routine checking necessary in the use of the occlusive cap. The International Planned Parenthood Federation, 69 Eccleston Square, London, S.W.1, can give information about the facilities available for obtaining advice on the use of contraceptives and their availability in any country in the world.

SYLVIA DAWKINS, M.B., B.S.

Detergents and Septic Tank Drainage

QUERY.—Having moved down here from London, I am living in an old Sussex cottage with a

septic tank drainage system, which has been recently reconstructed and is in good working order. All effluents pass through the tank—bath water, excreta and kitchen waste water from washing up.

Would you be kind enough to tell me whether the use of detergents in the kitchen destroys the bacterial action in the septic tank, and is likely to cause trouble there?

REPLY.—Certain types of synthetic detergents are more liable than others to influence adversely the oxidization of sewage. The chances of trouble vary inversely with the efficiency and speed of oxidization. Some detergents such as alkyl sulphates and sulphonated fatty esters and amides are readily oxidized biochemically; others, such as alkyl aryl sulphonates and alkyl phenoxy polyglycols, are relatively resistant to biochemical oxidization.

The significance of local conditions, including the precise nature and capacity of the septic tank and the particular treatment, including the frequency of removal of sludge and scum and the manner of disposal of the effluent, together with the type and extent of use of the synthetic detergents is such that any authoritative opinion requires assessment of each of the various factors on the spot. Appropriate advice would be most readily available from the local surveyor or public health inspector.

C. METCALFE BROWN, M.D., D.P.H.

Antivenene in Snake-bite

QUERY.—I read with interest Dr. Seaton's account in your April issue (p. 473) of the emergency treatment of snake-bite. There is one point in treatment which he does not mention: How long after the bite does it continue to be worth while to give antivenene?

When working in South Africa last year, Africans often came to me who had been bitten 6, 12, 24 or 48 hours before. I usually gave antivenene but I often wondered if it was not a waste of time and serum.

REPLY.—Little benefit is to be expected from the use of antivenene after a lapse of more than a few hours from the time of the bite. Thereafter the decision whether or not to use it should be made according to the circumstances of the case. If serious symptoms of poisoning are present it cannot justifiably be withheld, but there will be many cases seen 12 or more hours from the time of the bite who need nothing but reassurance.

D. R. SEATON, M.B., M.R.C.P., D.T.M. & H.

Dental Hæmorrhage

DR. T. J. MUCKLE writes:—I quite agree with Mr. Winstock (*The Practitioner*, April 1959, p. 513) that the first necessity in dealing with primary dental hæmorrhage is the removal of the clot. But I am surprised that he did not mention the painless effects of heat and cold before advocating chomping on an already tender gum margin. Grandma's remedy of ice or even cold water may suffice, but its styptic effect sometimes passes off as the gum warms back to body temperature. Unless the cold period has been long enough to allow firm adherence of clot to intima, the clot will be washed off as the vessel wall dilates up and away from it.

Strong heat is much better: although it will at first increase the bleeding, it shortly encourages retraction of the vessel ends and also speeds the clotting process. But its great merit is that when this thermal effect has worn off the gum now *cools* back to normal body temperature. Thus the terminal event of the heat treatment is vasoconstriction, as against vasodilatation after the cold. Blood flow tends to fall and the containing vital tube clamps down ever more firmly upon its inhabitant clot.

This method makes physiological sense. It is readily available in most households, simple, pleasant and convenient to use as a first line of defence and, I can testify, works 'like a charm' in most cases.

REPLY.—These comments are very pertinent and the treatment advocated well known and well tried. The purpose of my article, however, was to impart to medical practitioners some current useful measures to assist them to arrest dental hæmorrhage. Had the article been addressed to the layman in a weekly magazine I would probably have advised the homely remedies which Dr. Muckle so rightly mentions. I was assuming, however, that the patient had already tried the usual hot-and-cold applications treatment which is a traditional home-made approach to the matter. By the time the patient arrives in hospital or at his doctor's surgery, he has already lost a greater or lesser amount of blood, has been in the usual post-extraction pain for several hours and almost certainly has not eaten or had anything to drink for many hours. He is, in fact, very near, if not already in, a state of nervous and physical exhaustion and complete syncope is not far off.

In these circumstances, I do not feel that the doctor is justified in attempting to arrest the bleeding by the time-consuming method of hot applications to the socket (I am not sure how this can be done effectively with a subject not in the best possible condition for cooperation anyway), when he now has at his disposal very reliable therapeutic means, which require the minimum effort and the minimum cooperation from the patient.

I quite agree that exerting pressure on a tender gum is not very pleasant but, unfortunately, an injection to obtain local anæsthesia is an added trauma to the apprehensive patient and is also inclined to give a false picture of hæmostasis because of the local anæsthetic plus local vasoconstriction properties of present-day local anæsthetics. In any case, biting on a collapsible gauze swab does not exert severe pressure on the gum margins and the rewards more than compensate for the slight discomfort.

DONALD WINSTOCK, M.B., B.D.S.

PRACTICAL NOTES

Antibiotics and Chronic Bronchitis

'ALTHOUGH continuous daily tetracycline therapy may be preferable in certain advanced cases' of chronic bronchitis, 'intermittent treatment offers a reasonable and less costly alternative with a wider field of application', according to E. N. Moyes and S. Z. Kalinowski (*Tubercle*, April 1959, **40**, 112). Their conclusions are based upon a clinical trial, in which 25 patients were given tetracycline, 1 g. daily for seven days, followed by courses of 1 g. daily for five days taken at the first signs of symptomatic determination, and another group of 25 were given tetracycline 1 g. daily for seven days followed by 750 mg. daily for four months. In this latter group 15 (60%) of the patients obtained material benefit, compared with 10 (48%) of the 21 patients who were available for follow-up in the intermittent tetracycline group. In both groups 'there was a considerable reduction in the time lost from work compared with the previous winter'. On the question of cost, it is noted that the cost of four months' treatment is £25 per patient on hospital treatment prescription and £34 when prescribed outside hospital, whereas the cost per course in the intermittent method of treatment is 28*s.* 4*d.* The effect of erythromycin in the chemoprophylaxis was also investigated and the conclusion is reached that 'this antibiotic has no place in the routine treatment of chronic bronchitis'. The one side-effect encountered was diarrhœa: this occurred in 28 (30%) of the 93 patients who completed the trial, with an even distribution among those who received tetracycline and those who received erythromycin. In 13 it was mild but the other 15 had frequent watery stools for at least seven days, and treatment had to be temporarily stopped or modified in five.

Treatment of the Common Cold

"DILACOL' is 'of use in combating the symptoms of the common cold', according to Tom McEwan (*Scottish Medical Journal*, April 1959, **4**, 199), of the University Department of Medicine, Royal Infirmary, Glasgow. In his opinion 'it appears at the present moment, to be the drug of choice for use in large industrial concerns, or closed communities, in an attempt to reduce the spread of acute coryza'. 'Dilacol' contains buphenine (1.5 mg.), propyl salicylamide (60 mg.) and quinine hydrochloride (50 mg.). Buphenine is a peripheral vasodilator, and propyl salicylamide and quinine provide analgesic and antipyretic effects. The trials upon which the author's conclusions are based were carried out on 160 hospital nurses over a two-year period. In the initial trial, using a dosage of 2 tablets thrice daily for two days, and then 1 tablet thrice daily for three days, the percentage cleared with 'dilacol' was 76%, compared with 8% in the control group—a statistically significant difference. In a second group, given 2 tablets four times daily for the first four days, an even better result was obtained, but 20% of the subjects complained of headache. Almost equally good results were obtained with a dosage of 2 tablets ×4 for two days, and then 1 tablet ×4 for two days, but only two of the 50 subjects complained of 'side-effects': headache and tinnitus in one case, and palpitations in the other. It is therefore concluded that this last particular dosage-schedule is 'the optimum average dosage'.

Phenylbutazone-Steroid Therapy

PROMISING results are reported by M. A. Moriarty (*Journal of the Irish Medical Association*, April 1959, **44**, 114) from the use of a combination of phenylbutazone and prednisone in a small series of 10 patients with 'rheumatic and other painful conditions'. The preparation used was 'delta-butazolidin', which contains 1.25 mg. of prednisone and 50 mg. of phenylbutazone ('butazolidin') per tablet. The usual initial dose was 3 tablets daily, though one patient with severe post-herpetic neuralgia was given 8 tablets daily. The maintenance dose was 1 to 3 tablets daily. The series included five cases of rheumatoid arthritis, and one each of osteoarthritis, ankylosing spondylitis, post-herpetic neuralgia, Dupuytren's contracture, and painful shoulder. In all 10 cases there was 'satisfactory pain relief (and, where there was joint involvement, increased movement)'. The longest period for which treatment was continued was sixteen weeks, and it is stated that

'no side-effects were seen in any of the patients treated'. The view is expressed that 'the proportions in which the two substances are present in "delta - butazolidin" seems an eminently suitable one, both for introductory and maintenance treatment'.

Lobeline and Smoking

FURTHER evidence is adduced by G. W. Rapp and his colleagues (*American Journal of Medical Sciences*, March 1959, **237**, 287) that lobeline is of value as a smoking deterrent, provided it is suspended in a buffering base. (For their previous report see *The Practitioner*, 1955, **175**, 648.) When lobeline is suspended in an inert vehicle, such as corn starch, it is poorly absorbed. In a buffered vehicle consisting of tricalcium phosphate and magnesium carbonate (slow-acting and fast-acting antacid compounds, respectively), however, absorption is rapid and consistent. It is claimed that the blood lobeline level is 'directly related to the effectiveness of this agent in acting as a curb to smoking', and that the effective blood level is 100 to 140 mg. of lobeline per 100 ml. of blood. Such levels they obtained from the use of a preparation ('bantron') containing 2 mg. of lobeline sulphate, in the buffered vehicle already described, per capsule. The dosage was one capsule thrice daily after meals. They investigated this regime in two groups of smokers: 25 who did not wish to give up smoking, and 28 who wanted to stop smoking or at least to cut down the amount they smoked. In both groups a considerable degree of success was achieved—but in different ways. In the case of those who did not want to stop smoking there was no decrease in the number of cigarettes smoked, but a definite decrease in the amount of each cigarette smoked—as assessed by the weight of the cigarette after being stubbed out. Thus, the average weight of tobacco actually smoked per day fell from 11.5 to 4.1 g. In the case of those who wished to stop, or reduce smoking, the average number of cigarettes smoked daily fell from 18.6 to 4.6.

Erythema Nodosum

IT is now agreed that there are three main causes of erythema nodosum: tuberculosis, streptococcal infection, and sarcoidosis. In an analysis of 70 cases seen in an area of south-east England during the last seven years C. M. R. Vesey and D. S. Wilkinson (*British Journal of Dermatology*, April 1959, **71**, 139) report that 45.6% of their cases were of proven or presumptive streptococcal origin, 5.6% were tuberculous, 35.7% accompanied sarcoidosis, and 13% were of mixed or unknown origin. The female:male sex ratio was 3.4:1. The age incidence varied considerably. In general, tuberculous cases occurred predominantly in childhood; streptococcal had a wide span from childhood to old age, but predominantly from 25 to 50. In discussing the cases associated with sarcoidosis, reasons are given for differentiating those with only or predominantly hilar-gland enlargement from those with generalized sarcoidosis. Among the streptococcal group are a group of seven middle-aged women with erythema nodosum following an exacerbation of chronic bronchitis. The practical significance of this group is that it may be confused with sarcoidosis. Attention is drawn to the fact that the presence of otherwise unexplained loss of weight, when associated with cough and dyspnœa, is 'very suggestive of sarcoidosis'. Bruising is considered to be a characteristic feature of the condition. It was present in all the cases in this series. On the other hand, it may be absent when erythema nodosum is an early feature of sarcoidosis and the lesions rapidly become infiltrated with cellular sarcoid deposits.

Caterpillar Dermatitis

IN recording an outbreak of 600 cases of caterpillar dermatitis in a group of 3000 Israeli soldiers, L. Ziprkowski and his colleagues (*Israel Medical Journal*, January-February 1959, **18**, 26) discuss the salient features of this condition. The causative agent was *Thaumatopœa wilkinsoni*, which was introduced into Israel from Cyprus in 1940, and is found in pine forests. The groups involved in the outbreak described by Ziprkowski were encamped in a pine grove and the rash, accompanied by severe itching, appeared a few hours after their arrival in the grove. The dermatitis was caused by the hairs on the larvæ of the caterpillar. These are 0.15 to 0.5 mm. long, and 0.003 to 0.006 mm. thick, and each larva is said to have 630,000 hairs. During pupation the hairs fall off, and some are used to build the cocoon. Neither the pupæ nor the adult caterpillars possess these hairs. The poison in the hair is effective for a long period, the same skin reactions having been obtained with hairs left for twelve years as with living hairs. This means that direct contact with larvæ is not essential, but that the dermatitis can be acquired from contact with cast-off hairs lying on the ground in pine groves infested with the caterpillar. The skin lesions were quite unlike those caused by the sting of an insect, and resembled more an urticaria. There was no systemic disturbance and the rash disappeared eight days after the patients left the infested area.

See-Saw Nystagmus

SEE-SAW nystagmus is a rare form of nystagmus in which one eye moves up while the other one moves down. In reporting two cases, O. A. Jensen (*British Journal of Ophthalmology*, April 1959, **43**, 225) states that only three other cases have been reported. One of his cases was a male, aged 55, who suddenly developed a feeling of numbness in the left half of the tongue, spreading to the left side of his face, giddiness and diplopia. He did not lose consciousness. A diagnosis was made of a vascular occlusive lesion of the left posterior inferior cerebellar artery—the so-called Wallenberg syndrome. He ultimately made a complete recovery. The nystagmus disappeared within two days. The other was a 66-year-old alcoholic male who was admitted to hospital in an inebriated condition. In addition to the see-saw nystagmus he had involvement of the oculomotor nerve and a right-sided extensor plantar response. The following day his condition was much better but he discharged himself from hospital before he could be fully investigated. It was considered, however, that he, too, had had a thrombosis of the brain-stem arteries. Although the pathogenesis of this condition is unknown, it is suggested that it 'appears to occur in the presence of lesions in the brain stem, particularly if there is involvement of the upper parts of the medial longitudinal fasciculus, perhaps in the area of the posterior commissure'.

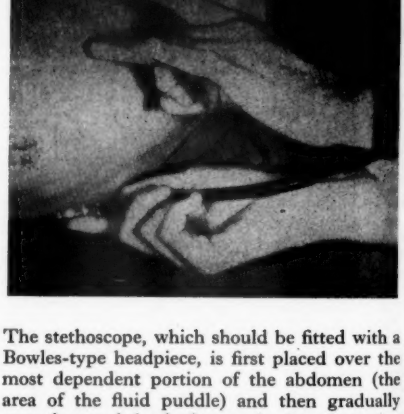
Antibiotics in Cosmetics

A WARNING against the potential danger of incorporating antibiotics in cosmetics has been issued by the Committee on Cosmetics of the American Medical Association (*Journal of the American Medical Association*, April 4, 1959, **169**, 1626). The view is expressed that 'under no circumstances should the antibiotics generally useful in the treatment of systemic infection be incorporated in cosmetics because of the risk of inducing sensitization to antibiotics which may be required for life-saving measures, or of inducing bacterial resistance to them. It is admitted that these risks are less significant in the case of antibiotics, such as neomycin, polymyxin and tyrothricin, which are not usually given systemically, but attention is drawn to their potentialities as skin sensitizers, and to the known nephrotoxicity of some of them. On the more general aspect of the problem the statement is made that 'there is no evidence that constant degerming of the skin (except to reduce axillary odours), such as would presumably occur with the widespread use of antibiotics in cosmetics, is necessarily always or even frequently desirable'. The final conclusion is that, except for the deodorant action of antibiotics in reduci axillary odours, 'their widespread use in co metics could well represent an increased risk general health as well as to certain hype sensitive individuals'.

The Puddle Sign

THE puddle sign, according to J. D. Lawson A. S. Weissbein (*New England Journal Medicine*, March 26, 1959, **260**, 652) is 'a ver reliable physical sign' for the detection of mini mal ascites. They have found it consistentl present with as little as 120 ml. of peritonea fluid, and it is not affected by marked obesit or the presence of considerable fluid in th lumen of the bowel. The method of eliciting i is as follows:—

'The patient lies in the prone position f five minutes. He then assumes a position o "all fours" so that the middle portion of th abdomen is dependent. One flank is percussed by repeated, light flicking at a constant intensity.



The stethoscope, which should be fitted with a Bowles-type headpiece, is first placed over the most dependent portion of the abdomen (the area of the fluid puddle) and then gradually moved toward the flank opposite the percussion site. A positive sign consists of a marked change in the intensity and character of the percussion note as the stethoscope is moved toward the opposite flank. To the ear, the intensity of the note seems to increase, and a point of demarcation is noted that correlates well with the amount of fluid present. The patient then sits up, the examiner holding the stethoscope on what was the dependent part of the abdomen. If the percussion note then becomes loud and clear, the initial impression is corroborated'.

REVIEWS OF BOOKS

rgery of the Colon. By E. S. R. Hughes, M.D., M.S.(Melb.), F.R.C.S., F.R.A.C.S. Edinburgh: E. & S. Livingstone Ltd., 1959. Pp. viii and 416. Figures 234. Price 63*s*.

book can be recommended without hesita- ı to practising surgeons, and to those studying or the Fellowship. Mr. Hughes's previous book ı 'Surgery of the Anus, Anal Canal, and ectum' stepped into immediate favour when it as published two years ago, and this one will ive an equal welcome. This is a personal text- ook, giving the author's views based upon his wn very considerable experience, and illus- ted by his own pen-and-ink drawings. These wings, and the many photographs of speci- ens, are among the best features of the book. e writes as one who has made the diseases of ne large bowel his special study rather than as a urgeon, and two of the best chapters are those n chronic constipation and chronic diarrhœa, nto which surgery hardly enters. Chapters VIII on ulcerative colitis and IX on regional colitis re as good a review of this important con- emporary problem as can be found anywhere.

Cancer naturally looms large in any textbook dealing with the colon, and the three chapters dealing with cancer occupy a quarter of the book. They are clear and helpful. By devoting the first to general considerations, and treating cancer of the left and the right half of the colon in separate chapters, the author has been able to give an admirably clear account of the diagnostic features and the technical problems of these quite distinct clinical entities.

Cancer of the Skin. By John C. Belisario, C.B.E., E.D., M.D., Ch.M., D.D.M. London: Butterworth & Co. (Publishers) Ltd., 1959. Pp. xvii and 335. Figures 201. Price 50*s*.

This excellent and comprehensive monograph is based upon the author's vast experience with pre-cancerous conditions and the common skin cancers. As might be expected, the clinical description of rodent ulcer (which the author would like to call rodent carcinoma) is full and admirable. Nine clinical types are recognized and fully illustrated. The emphasis on treatment is almost entirely radiological. The methods used are clearly and succinctly described. A striking innovation is his report of six years' treatment using a combined attack with the cautery and painting with 50% podophyllin. This will make an appeal to many who do not have the benefit of x-ray apparatus. 'Scalpel Surgery' receives little attention and mainly with reference to cases with bone involvement. This is perhaps a little out of balance since in quite a number of cases a surgical excision is a simple and satisfactory method of treatment.

Although, rightly, the main portion of the book deals with rodent ulcer and squamous carcinoma, there is an excellent chapter on melanoma. Pre-cancerous conditions are fully dealt with and also the comparative rarities such as sarcoma and the reticuloses. References account for 37 pages so the reader is assured of a round-the-world survey of opinion.

Monograph on Neoplastic Disease at Various Sites. General Editor: D. W. Smithers, M.D., F.R.C.P., F.F.R. *Vol. I—Carcinoma of the Lung.* Edited by J. R. Bignall, M.D., M.R.C.P. Edinburgh: E. & S. Livingstone Ltd., 1958. Pp. xii and 298. Figures 62. Price 55*s*.

The intention behind these monographs is 'to present a detailed clinical picture of the range of neoplastic disease taking place in one particular organ or tissue at a time'. Volume I does this for carcinoma of the lung and eight contributors have taken part, each in his own particular field. Mortality statistics and causation, the pathological types and the method of spread, the clinical course of the disease, and, finally, treatment by surgery, radiotherapy and chemotherapy are the main subdivisions. This book provides a valuable study of a disease which, because of its alarming increase in recent years, has become important to most practical clinicians irrespective of their specialty. It can be recommended as an authoritative and well-illustrated account of the subject.

Cancer of the Pharynx, Larynx and Œsophagus and its Surgical Treatment. By Ronald W. Raven, O.B.E., T.D., F.R.C.S. London: Butterworth & Co. (Publishers) Ltd., 1958. Pp. xiv and 302. Figures 189. Price 67*s*. 6*d*.

This is a useful and comprehensive book dealing with cancer of a limited area. It is written by a surgeon and therefore has a bias towards surgery, although the relative value of deep x-ray therapy is given full consideration, particularly in the areas most suitable for conservative treatment. In the oropharynx and hypopharynx the author describes in detail the removal and plastic reconstruction necessary. Trotter's aphorism is again stressed that the treatment of cancer is not the removal of a

specific organ but the curing of the disease. A chapter is given to the anæsthesia suitable for each area and some pages to the latest techniques in tracheotomy. That still incompletely understood condition of stenosis in the upper œsophagus in anæmic females, with the name of Paterson-Kelly now replacing the old name of Plummer-Vinson, is fully discussed and, although no conclusion is reached, a valuable survey is made of the up-to-date theories. The section on the larynx is covered in thirty pages. The tumours are divided into those arising in the true glottis or vocal cords—the commonest site, in the subglottic region, and in the supraglottic area—arising from the ventricle or false vocal cords—this is the least frequent situation. The section on the œsophagus follows the generally accepted principles.

This book, well illustrated and on excellent paper, is intended for the surgeon operating in that area. For him and for the young surgeon working for higher surgical qualifications, it is essential reading. It is a first-class surgical textbook, a credit to the author and the publishers.

Understanding Your Patient. Edited by SAMUEL LIEBMAN, M.D. Philadelphia: J. B. Lippincott Co.; London: Pitman Medical Publishing Co. Ltd., 1958. Pp. viii and 170. Price 40*s.*

THIS volume is the third of a series aimed at helping the medical practitioner towards a better understanding of his patients, and consists of essays by distinguished American psychiatrists, in which are discussed the emotional problems of early development, of the school-age child, of the teenager, of the adult and of the grandparent. 'Counselling', both before and after marriage, is fully considered. The amount of 'tender, loving care' which these essays recommend to be lavished on the awkward schoolboy, the uncomfortable bride and the bewildered grandparent is quite astonishing. The best of these chapters develops the thesis that emotional and social isolation and deprivation in the early months and years of life, e.g. in a hospital crib, is a true deficiency disease which does not permit the normal growth of the human personality and intellect, and that the deficit may be permanent. 'It must be emphasized', says Dr. Lauretta Bender, 'that a rejecting parent, an inadequate, inconsistent or even cruel parent, or what has lately been called a "cold family climate", will not produce this same inhibition in personality maturation'. Schizophrenia in the child is considered to be a maturational lag at the embryonic level, genetically determined, but in this and in many other developmental syndromes, the prognosis is more than likely to be favourable.

It will be a great advantage in reading this book to be thoroughly familiar with psychiatric terminology. Some day perhaps it will come to earth in monosyllables.

Orthopedic Diseases. By ERNEST AEGERTER, M.D., and JOHN A. KIRKPATRICK, JR., M.D. Philadelphia and London: W. B. Saunders Co., 1958. Pp. xii and 602. Figures 354. Price 87*s.* 6*d.*

This is a book for the specialist. It is an up-to-date account of the pathology of bone disease that will be met with by the orthopædic surgeon. The section on bone tumours is especially valuable because in it tumours are to some extent reclassified according to modern concept and nomenclature. The operating surgeon, on reading the part necessary for his purpose, will equip himself with much statistical and histological information. The authors, however, do not go to great pains in their advice on treatment, and so the operating surgeon may feel deprived of the advice of which he is in most need—namely how to treat the patient.

The book is written by a pathologist and a radiologist, and as far as it goes is the best of its kind that is available at the moment. It will find a place in the library of the orthopædic surgeon who prides himself on the amount of his knowledge of bone pathology. For the teacher of orthopædic surgery it will be invaluable as a ready reference for common and obscure conditions. The book is beautifully produced and profusely and usefully illustrated.

Iron in Clinical Medicine. Edited by RALPH O. WALLERSTEIN, M.D., and STACY R. METTIER, M.D. University of California Press; London: Cambridge University Press, 1958. Pp. xiii and 283. Price 45*s.*

THIS is an attractive and lucid presentation, by a number of eminent contributors, of iron metabolism and its significance in relation to the treatment of hypochromic anæmia. A brief and interesting historic outline is followed by discussion of the parts played in assimilation, transport and storage of iron by the serum transferrin and the tissue ferritin and hæmosiderin. It is made clear that the details relating to the absorption of iron by the intestinal mucosa are scarcely known, and that the concept of a 'mucosal block' controlling assimilation requires modification in the light of recent work. The problems relating to the etiology of hæmosiderosis and hæmochromatosis and the different manifestations of iron-storage disease are clearly set forth. The conflicting views on

whether excess iron promotes tissue damage, or whether tissue damage precedes iron accumulation are presented. The sections on therapeutic management of hypochromic anæmia are concisely and lucidly written. The importance of blood volume changes in pregnancy, either masking or exaggerating an anæmia, are emphasized, and evidence is given of the unconvincing beneficial effect of parenteral iron given to patients with hypochromic anæmia associated with rheumatoid arthritis. A chapter on the pharmacology of iron preparations is of particular interest. The lesser toxicity of iron dextran as compared with saccharated iron oxide is attributed to its greater stability.

Diagrams are numerous and most are simple, but in the sections devoted to ferritin and ferrokinetics, some figures are confusingly complex. Good bibliographies are included in the relevant sections, but there is no index. The book can be recommended to all hæmatologists but is probably somewhat heavy going for the general physician except for reference purposes.

So You Have Glaucoma. By EVERETT R. VEIRS, M.D. New York and London: Grune & Stratton, 1958. Pp. vii and 64. Price $2.75.

How much should a patient be told about his disease and its treatment? There must be few doctors who adopt the 'don't worry, you are in my care' attitude which used to be more common in countries other than our own, but many deprecate the popular demand for detailed medical information in the press and on the other. 'A little learning is a dangerous thing' and no one can hope in an hour or two to acquire the information and breadth of judgment for which a lifetime is inadequate, so it is important that the 'little learning' should be correct and confined to essentials.

This book explains in the simplest language the anatomy and physiology of the eye and in some detail the pathology of various types of glaucoma. It should be interesting and valuable to the more intelligent glaucoma subjects and doubtless also to those with a tendency to glaucoma-phobia for whom it is contraindicated. It takes good care, however, to avoid describing the abnormal changes in the visual fields which patients might otherwise begin to imagine they are developing. The two lessons it brings home are that glaucomatous visual loss, though preventable, is permanent and irreversible and that the ophthalmologist's instructions regarding the use of drops and drugs must be carried out meticulously if the effect of treatment is to be accurately assessed. Finally it is the answer to the patient who at the end of a long and complicated examination asks 'Just tell me, exactly what is glaucoma?'

The History and Philosophy of Knowledge of the Brain and its Functions. Edited by F. N. L. POYNTER, PH.D., F.L.A. Oxford: Blackwell Scientific Publications, 1958. Pp. x and 272. Illustrated. Price 22*s.* 6*d.*

THIS symposium was held in London as an historical introduction to the First International Congress of Neurological Sciences in July 1957. Its purpose was to review the age-long endeavours to associate the 'mental' with the neurophysiological. Concepts of the brain in classical antiquity, mediæval and more recent times are dealt with by several authorities. These ancient philosophers, however, were without the most elementary knowledge of the structure of the nervous system so that their ideas, though of great interest, are now of little help to us. The more modern era is ushered in by discoveries regarding electricity and the nervous system, the history of which is well presented by Dr. Mary Brazier; finally, Dr. Chandler Brooks brings us up to date and shows the overwhelming influence of the development of the neurone theory of brain structure, the discovery of the reflex pathway, of the synapse and of the peculiar properties of the cell membrane.

This is an appropriate introduction to future congresses, whose proceedings in a subject that is advancing so quickly will at times be breathtaking.

Psychiatry and the Public Health (Heath Clark Lectures 1957). By G. R. HARGREAVES, O.B.E., M.SC., M.R.C.S., L.R.C.P. London: Oxford University Press, 1958. Pp. 118. Price 12*s.* 6*d.*

PSYCHIATRY has been developing rapidly in recent years and has been subjected to frequent changes in theoretical orientation. It is unusual to find an author who, in the midst of this flux, has taken time to think out the present position of psychiatry in its historical perspective. With new responsibilities, extending far beyond the traditional scope of psychiatry, looming up as a result of imminent legislation, this should prove a valuable review. The author has had exceptional experience of the social responsibilities of psychiatry in many countries. He emphasizes the importance of prevention and sees the psychiatrist of the future yielding his burden as regards this aspect of his work more and more to the general practitioner and to the public health officer. The evidence he adduces and the arguments he uses convince the reader of the validity of his conclusions. The book may well come to be regarded as a classic.

NEW EDITIONS

Treatment of Cancer and Allied Diseases. Vol. I. *Principles of Treatment*, edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S., second edition (Pitman Medical Publishing Co. Ltd., £8).—This is the first volume of a book, or a 'series' as the publishers describe it, which is to be completed in nine volumes, and devoted to the clinical aspects of the management of malignant disease. The subsequent volumes will deal with the subject on a regional basis. Practically all the fifty-five contributors are American workers, the only two British contributors being Miss Constance Wood, who contributes the chapter on 'The clinical application of the radium element pack', and Dr. J. L. Dobbie who writes on 'Methods of applying radium in cancer therapy'. This first volume is a most comprehensive review of the subject, including a section on cancer prevention and one on 'Reporting end results of cancer treatment'. It will prove a valuable work of reference for all concerned with the treatment of cancer.

Practical Dermatology, by George M. Lewis, M.D., F.A.C.P., second edition (W. B. Saunders Co., 56*s*.).—In the second edition of this book, which is designed as a text for medical students, a practical guide for general practitioners, and 'an aid in orientation for other specialists', a short chapter has been added giving brief comments on virology, pathology, physiology and mycology in relation to dermatology. Emphasis throughout is on means to accurate diagnosis and selection of appropriate treatment. The teaching is sound and the author achieves his purpose with concise clinical descriptions of the more common skin diseases and clear directions for dealing with them. Few words are wasted on experimental methods or unproven remedies but where necessary he speaks firmly on what should not be done. Sufficient histopathology is included if it helps in the understanding of the disease process. There are good reviews of premalignant and malignant tumours, including lymphoblastoma, of benign growths and cystic lesions, of metabolic disorders and the skin, of the skin as a mirror and of interrelationships between skin and systemic disease. The comprehensive dermatological formulary contains helpful warnings on the irritant or sensitization risks of certain remedies. The photographs (all in black and white) are excellent, as is the general presentation.

Wolff's Diseases of the Eye, fifth edition, revised by Redmond J. H. Smith, M.S., F.R.C.S., D.O. (Cassell & Company Ltd., 42*s*.).—This work has been a standard textbook for over twenty years, and one which has been popular because of its easily read text and ample illustrations. Probably it is the best students' textbook of ophthalmology in the English language, and is sufficiently comprehensive for all general examinations and the Diploma in Ophthalmology. The fifth edition has a new author and, whilst all chapters have been reviewed, only a few have as yet been brought fully up to date. Ophthalmology, like other branches of medicine, has made rapid strides in recent years and it may not be long before a sixth and even better edition of this work will be published.

Lehrbuch der Geburtshilfe, by Prof. Dr. Heinrich Martius (Georg Thieme, DM. 59.70).—This book comes from the masterly pen of an eminent German gynæcologist. In its fourth edition within a decade many, though perhaps not all, important recent advances in obstetrics are mentioned. Some subjects, such as the anatomy and physiology of labour, multiple pregnancy, congenital malformations, breast, puerperium, contracted pelvis and the management of disproportion, have been dealt with superbly, but to conduct a trial labour until the cervix has been fully dilated for two hours is perhaps going a little far. Hyperemesis, inertia and the etiology of toxæmia are outlined too briefly and the author's views on heart disease in pregnancy are rather gloomy. The author proves to be fully conscious of his function as a teacher: he emphasizes the anatomical and physiological principles underlying the various obstetric conditions; abandons the accuracy of photographs in favour of a vast number of excellent didactic illustrative drawings by Käthe Droysen; gives practical advice for the young obstetrician; and makes a clear distinction between treatment in hospital and what is feasible in the patient's home.

The contents of the July issue, which will contain a symposium on 'Diseases of the Veins,' will be found on page A 122 at the end of the advertisement section.

Notes and Preparations see page 783.
Notes from the Continent see page 787.
Fifty Years Ago see page 789.
Motoring Notes see page A 93.
Travel Notes see page A 97.

INDEX AND BINDING CASES

The index to Vol. 182 (January-June, 1959) will be forwarded to all subscribers with the July issue. Binding cases for this and previous volumes are available in green cloth with gilt lettering, price 6*s*. each, post free. The cases are made to hold 6 copies after the advertisement pages have been removed; they are not self-binding. Alternatively, subscribers' copies can be bound at an inclusive charge of 15*s*. per volume; this includes the cost of binding case and return postage.

She's on Nilergex
TRADE MARK

the non-sedative antihistamine

'Nilergex' is a potent antihistamine for the symptomatic relief of allergic conditions including hay fever; vasomotor rhinitis; allergic dermatoses and food allergies; insect bites and stings.

'Nilergex' is outstandingly free from side effects. It is the most suitable antihistamine for routine use in ambulant patients of all ages who are following their daily occupation and need to be alert.

Available as 'Nilergex' Tablets 4 mg., 'Nilergex' S.A. (Sustained Action) Tablets 12 mg., and 'Nilergex' Syrup 2 mg. per teaspoonful (3.5 ml).

Nilergex
TRADE MARK

Basic N.H.S. cost : 4/- for 50 x 4 mg. or 20 x 12 mg. (Sustained Action) tablets and 3/4d. for 100 ml. of 'Nilergex' Syrup.

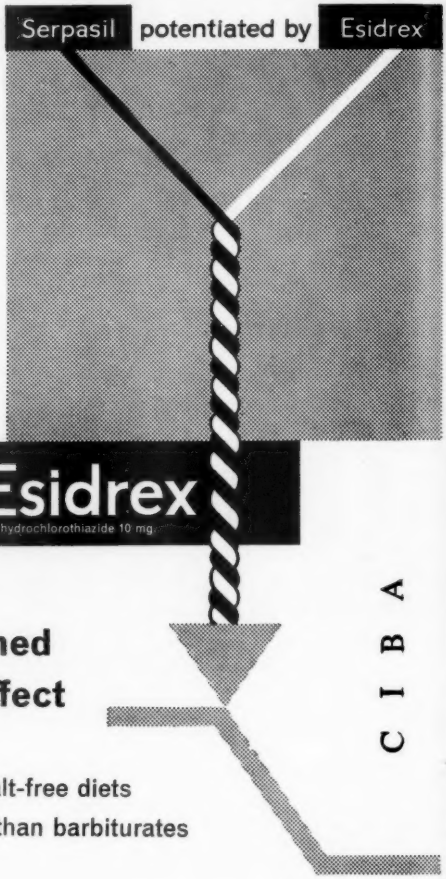
References: Arzneimittel-Forsch 1957,7,237 New York State J.Med., 1957,57,3329
Ann. Allergy. 1958,16,237

IMPERIAL CHEMICAL INDUSTRIES LIMITED Pharmaceuticals Division Wilmslow Cheshire

ICI

Ph.855

Rational combination for hypertension both with and without heart failure



Prompt and sustained antihypertensive effect

Salt depleting—supersedes salt-free diets
Calming and relaxing—better than barbiturates
Economical Well tolerated

Usual dose, three tablets daily.
Detailed literature available on request.
Available in 25's (Basic N.H.S. price 5s. 4d. + P.T.), 100's and 500's.

Serpasil and Esidrex are registered trade marks. Reg. user

CIBA Laboratories Limited, Horsham, Sussex.

1/9

NOTES AND PREPARATIONS

NEW PREPARATIONS

'AMINOSOL VITRUM' preparations for intravenous use are produced 'by enzymatic hydrolysis of casein and they contain a full complement of free amino-acids'. They contain 3.3 parts of 'aminosol' per 100 parts of solution. 'Aminosol-glucose vitrum' contains, in addition, 5 parts of glucose per 100 parts of solution, and 'aminosol-glucose-ethanol' contains, in addition, 5 parts of glucose and 5 parts of ethanol per 100 parts of solution. Available in bottles of 500 and 1000 ml., and also 100 ml. for pædiatric use. A complete range of oral preparations is also available in the form of powder, granules, tablets or syrup. (Paines & Byrne Ltd., Pabyrn Laboratories, Perivale, Greenford, Middlesex.)

'EBIMAR' tablets each contain 0.5 g. of 'ebimar', which is 'a specially purified sulphated polysaccharide (representing not less than 1000 Evans units of antipeptic activity)', and are intended for the treatment of peptic ulcer. The recommended dosage is 3 to 4 tablets to be sucked, chewed, or taken crushed four or five times daily between meals. Issued in containers of 100 and 500. 'Ebimar-Al' tablets contain 0.5 g. of 'ebimar' plus 0.35 g. of dried aluminium hydroxide gel B.P., and are issued in containers of 50 and 250. (Evans Medical Supplies Ltd., Speke, Liverpool, 24.)

'MILLICORTEN' tablets each contain dexamethasone which is said to be 7.5 times more potent than prednisolone in the treatment of 'all inflammatory and allergic conditions in which oral corticosteroids have proved effective'. Available as tablets of 0.5 mg. and 1 mg., in packs of 25, 100 and 500. (CIBA Laboratories Ltd., Horsham, Sussex.)

'SERPASIL ESIDREX' tablets each contain 0.15 mg. of reserpine and 10 mg. of 'esidrex' (hydrochlorothiazide) and are intended for the treatment of essential hypertension, in which they are said to potentiate the effect of ganglion blocking drugs, and 'undesirable fluctuations of blood pressure' between doses of these agents are reduced. Issued in packs of 25, 100 and 500. (CIBA Laboratories Ltd., Horsham, Sussex.)

'VALOID' ampoules each contain 50 mg. of cyclizine lactate and are indicated primarily for the prophylaxis and treatment of postoperative nausea and vomiting and also in other types of intractable vomiting when oral therapy is impracticable. Available as 1-ml. ampoules in boxes of 5. (Burroughs Wellcome & Co., The Wellcome Building, Euston Road, London, N.W.1.)

PHARMACEUTICAL NOTES

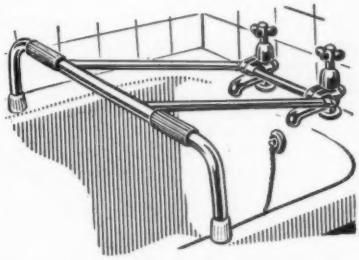
GLAXO LABORATORIES LTD. announce that 'predsol suppositories' have now been added to their range of prednisolone preparations. Each contains 5 mg. of prednisolone (as prednisolone disodium phosphate). They are intended for local treatment of inflammatory conditions of the rectum. Available in packs of 6 suppositories. (Greenford, Middlesex.)

JOHNSON & JOHNSON LTD. announce that their 'band-aid' range of first-aid dressings now includes a pack of ten plastic strips in a slim folder suitable for pocket or handbag, and a new cellophane-wrapped and sterilized elastic dressing strip dispenser for home use which is available in widths of 1½ and 2½ inches in lengths of 1 yard. (Slough, Bucks.)

WILLIAM R. WARNER & CO. LTD. announce the introduction of 'tedral' pædiatric suspension, containing the equivalent of half a 'tedral' tablet in each teaspoonful. (Eastleigh, Hampshire.)

NEW APPARATUS

'ECONOMIC' bath safety rails are especially useful for invalids and old people and can be attached to any bath fitted with conventional taps. They do not affect the taps in any way, no alteration to the bath is required, and they can be swung up over the bath when not in use.



The width from centre to centre of the rubber tips which rest on the bath is 25 inches (63.5 cm.), but different widths can be supplied to order, and special rails can also be provided for baths not fitted with conventional taps. (Charles Winn & Co. Ltd., Granville Street, Birmingham 1.)

MOBILE PHYSIOTHERAPY UNITS

THE Mobile Physiotherapy Service Association, which was inaugurated in 1946, has now four-

teen services associated with it in eleven counties. An increasing number of inquiries about the formation of further services is being received, according to the Association's recently published report for 1958, particularly from hospital management committees and old people's welfare committees. As the Association is entirely dependent upon voluntary support, the extent to which it can subsidize such services is limited by the amount of the financial support which it receives. As Dr. Doris Baker pointed out in her article on 'Domiciliary Physiotherapy' (*The Practitioner*, 1958, **180**, 316), there is an increasing need for facilities to bring physiotherapy to housebound patients. The type of service provided by the Association is that the fee for a visit, which is only arranged on the recommendation of a doctor, is 9*s*. to 17*s*., according to the distances to be covered. The maximum charge to a patient is usually a quarter to a third of the total cost, the balance being met by voluntary subscriptions and donations. Full details can be obtained from the General Secretary of the Association at 12 South Audley Street, London, W.1.

GUILDFORD CATHEDRAL

THE artist chosen to design the doctors' window for the nave of Guildford Cathedral is Miss Moira Forsyth, who has already designed the Rose Window over the altar. Contributions towards the cost of the window have so far totalled over £800, but this is just over half the sum required. Full details of the scheme for providing this window were published in our November 1958 issue (p. 552). So that, in the words of a fresh appeal issued by the sponsors of The Doctors' Cathedral Window Fund, 'the medical profession shall not lag behind others which are also contributing windows to the Cathedral, further contributions are urgently invited and should be sent to the secretary of the Fund: Dr. F. A. Belam, 1 Westfield, Epsom Road, Guildford, Surrey, as soon as possible'.

NON-INFLAMMATORY CLOTHING

SOME of the difficulties encountered in attempting to persuade people to use non-inflammable clothing material are discussed in a recent article in *The Financial Times*. 'Clothing and fabric stores report', it is said, 'that an upsurge of interest in flame-resistant fabrics often follows an accident, usually involving a child, which receives newspaper publicity, but that the interest is soon dissipated'. One of the difficulties is that of cost. The cotton fabric, 'wincyette', for instance, which is a common material for nightwear, is sold at 3*s*. 11*d*. a yard untreated, but at 6*s*. 11*d*. a yard when treated for flame resistance. Made up into a nightdress for a child the price difference is 19*s*. 11*d*. against 14*s*. 11*d*. In spite of the public indifference to the problem, many retailers are 'extremely alive' to the problem. Marks and Spencers, for instance, refuses to stock non-flame-resistant nightdresses in children's sizes. Great Universal Stores conducts tests on flame-resistant garments and fabrics which are more exacting than those laid down in the British Standards, whilst John Lewis has 'consistently attempted to sell flame-resistant fabrics but with disappointing results'.

THE PHARMACEUTICAL INDUSTRY AND RESEARCH

IN 1958, pharmaceutical manufacturers in the United States spent $170 million on research, compared with $127 million in 1957. This represents about 7% of their total sales, compared with 2% in industry in general. The amount contributed by the pharmaceutical industry to medical schools and hospitals, or to finance research in them, was $2½ million.

VITAMIN E AND STAMINA

THE following is an excerpt from the tenth annual report, for the academic year 1957-58, of the medical officer of the Student Health Service of The Queen's University of Belfast:—

'At the beginning of the year I learned that the phenomenal success of the Australian athletes, especially the swimmers, at the Melbourne Olympic Games was attributed in large measure to the giving of vitamin E. This is one of the well-known vitamins which has little use in general medicine and had certainly never been thought of in the above respect. In addition, to be manufactured in the required dosage as used by the Australians it would have cost approximately some £50-60 per individual. One of our largest drug houses was approached and agreed to furnish a limited supply for trial. With the whole-hearted cooperation of the Athletic, Swimming and Rowing Clubs a selected group was given the vitamin over some two months prior to the Empire Games. We were convinced, as were the students taking part, that it had a considerable effect in delaying muscle fatigue and thus increasing stamina and muscle endurance without any side-effects whatever. While not proof, of course, it was significant that the rowing eight qualified to represent Ireland at the Olympic Games, while four athletes and two swimmers were also chosen. This year it is proposed to make a statistically planned experiment to try and confirm the above impression. If proved of value, its use in other fields outside athletics where muscle endurance is of primary importance might well be justified'.

MEDICINAL MOULD

'AUGUST 5, 1900.—The more mouldy bread I give Mrs. R. the better she becomes. There must be something in the mould that prevents or kills germs.' This extract from the recently discovered diary of Dr. Frank Richmond, a Kansas general practitioner, must be one of the first authenticated records of the systemic administration of moulds for the treatment of infections. The lady in question had typhoid fever. The diary, the finding of which is recorded in *GP* (1959, **19,** 192), also contains a reference to a boy, aged 18 years, with acute tonsillitis, whose parents refused to give him mouldy bread. Dr. Richmond therefore removed the mould from the bread and gave it to the sick boy with aspirin in a capsule. The entry in his diary the next day is: 'Robert's improvement is unbelievable. . . . I shall give all my patients with fever and infections mould. If I should tell the other doctors about this, they would think I am crazy'.

FORTY YEARS ON

UNLIKE clinicians, statisticians love prognosticating. Two interesting features emerge from the Registrar General's forecast of what will be happening in 1998. One is that the present excess of 1,490,000 females will be reduced to 503,000. The other is that the proportion of the population of pensionable age, which is at present 14.7%, will reach a maximum of 17.9% in 1988 and then fall to 16.7% in 1998.

ADMISSIONS TO A GERIATRIC UNIT

IN an analysis of 530 consecutive admissions to the geriatric unit, Queen's Park Hospital, Blackburn, in the year ended March 31, 1958, J. Hennigan (*J. Irish med. Ass.*, 1959, **44,** 86) reports that the four commonest causes for admission were: cerebrovascular disease (29.6%), cardiovascular disease (18.7%), senile dementia (12.6%), and inoperable cancer (10.4%). Between them, these four groups of diseases were responsible for over 70% of the admissions. Of the 99 patients admitted on account of cardiovascular disease, just over one-half (52.5%) had hypertensive congestive heart failure, and just under one-quarter (23.2%) had coronary thrombosis. Attention is drawn to the relatively high incidence of asymptomatic hypertension in the entire series. Taking 170/100 mm. Hg as the upper limit of normality, 45% of both men and women had pressures above this level.

RABIES IN INDIA

THE recently published annual report of the Pasteur Institute of Southern India, Coonoor, for 1957, gives some indication of the extent of the rabies problem in India. During 1957 the Institute produced over 4 million millilitres of antirabic vaccine. A review of the period, 1946-57, when a total of 9,015 persons bitten by infective or presumably rabid animals were seen, shows that 8.58% of persons bitten by proved infective animals developed rabies in spite of having a complete course of treatment. The mortality rate in this group was 3.44%, compared with 50% among those who refused treatment. If all cases are taken into consideration—i.e. all those bitten by proved infective and presumably rabid animals—the mortality rate in the treated group was 0.14%. Of the 3,560 animals investigated as being responsible for these cases, 78% were dogs, 19% were jackals, and 1% were foxes.

THE HAW-HAW SYNDROME

THE 'haw-haw syndrome' is the name given by Keith Young (*E. Afr. med. J.*, 1959, **36,** 44) to a condition well recognized in Somaliland, and characterized by rectal impaction of the seeds of *Grewia tenax*, the Somali name for which is 'defarrur' or 'haw-haw'. The fruit of this small flowering shrub is commonly eaten by Somalis. When a large quantity is eaten raw, impaction of the seeds in the rectum is so common that the natives have designed a special instrument to remove them. This is a long, slender, curved spoon known as a 'fageh'. Details are given of two cases of the 'haw-haw syndrome': two Somali boys, aged 12 and 14 years respectively, who were admitted to hospital with a history of abdominal pain, vomiting and constipation for over a week. Examination revealed rectal impaction, which was relieved in each case by the removal of one kilogram of 'haw-haw' seeds.

NONAGENARIAN DENTISTRY

IN the correspondence columns of the *British Dental Journal*, dentists have recently been comparing notes as to the oldest patient they have fitted with dentures. The record to date is that of the dentist who successfully fitted an edentulous man of 98 years with dentures. He is closely followed by the dentist who removed six lower incisors from a man of 96, and fitted him with a lower denture. He was already wearing a full upper denture. Next comes the fitting of the denture for a 90-year-old in 1953, who is still fit and well.

A PORCINE PHARMACY

'THE Tientsin Second Food Processing Factory' according to the *Chinese Medical Journal* (1959, **78,** 305), 'has manufactured 48 valuable drugs and chemical agents' from pigs. Cholesterol, lecithin, and cephalin are obtained from the

brain; oxytocin, corticotrophin and 'anterior pituitary powder' from the pituitary; bilirubin and bile salts (used for the manufacture of methyltestosterone) from the gall-bladder; 'protein-rich meat paste' (for bacterial cultures) from the residue from the lard-making process; and cyanocobalamin from the fæces.

PUBLICATIONS

New and Nonofficial Drugs 1959, the annual publication of the Council on Drugs of the American Medical Association, contains descriptions of drugs generally available in the United States that have not been included in the *Pharmacopœia of the United States*, or the American *National Formulary* for 'a prior cumulative period of twenty years'. It thus includes all the newer drugs at present in use provided these have been approved by the Council on Drugs. (Pitman Medical Publishing Co. Ltd., price 30*s*.)

Postgraduate Training in the Public Health Aspects of Nuclear Energy and *Introduction of Radiation Medicine into the Undergraduate Medical Curriculum* represent, respectively, the fourth (no. 154) and fifth (no. 155) reports of the expert committee on professional and technical education of medical and auxiliary personnel. The personnel of the committee differed in the two cases, but in each instance the membership was a widely based international one. Much is contained in both reports that will be of interest and significance to those concerned with keeping undergraduate and postgraduate curricula attuned both to the demands of advancing knowledge and to the increasing complexities of modern life. (H.M. Stationery Office, price 3*s*. 6*d*. and 1*s*. 9*d*.)

Medical Education is a bibliography on medical education covering material published between 1946 and 1955. Around 2,600 articles have been selected for inclusion. (H.M. Stationery Office, price 35*s*.)

A History of Cytology, by Arthur Hughes, PH.D., SC.D., lecturer in anatomy at Cambridge University, is well timed. The tremendous advances that have been achieved in recent years by the introduction of the electron microscope have tended to make enthusiasts lose their sense of historical perspective and, as Dr. Hughes points out, in no field of progress is such a perspective more essential than in microscopy. The non-expert, however, will find it an equally fascinating story, refreshingly free from technical jargon, and beautifully illustrated. (Abelard-Schuman, price 21*s*.)

Air Pollution, WHO Technical Report Series No. 157, is the fifth report of the Expert Committee on Environmental Sanitation, and shows a challenging recognition of this important problem of environmental sanitation. The effects of air pollution upon human health, on animals, on plants, and the economic and sociological effects are described, together with recommendations for the prevention and control of this increasing environmental evil. (H.M. Stationery Office, price 1*s*. 9*d*.)

A Symposium on the Evaluation of Drug Toxicity, edited by A. L. Walpole, PH.D., B.SC., and A. Spinks, M.A., PH.D., B.SC.—This symposium on drug toxicity was held in October 1957 to mark the inauguration of the new research laboratories of Imperial Chemical Industries (Pharmaceuticals Division). Many aspects of drug toxicity are discussed including morphological changes produced by drugs, and methods of testing for toxicity, and there are valuable chapters on the unpredictable and often serious effects upon the bone marrow and liver cells. The chapter on the allergic reactions to chemical substances is especially useful. The clinician who turns the pages of this book will be impressed by two points: the lack of understanding of the basic mechanisms involved in cellular injury by drugs, and the continued need for assiduous observation of the patient if serious side-effects are to be avoided when new remedies are used in therapeutics, no matter how carefully they have been 'screened' by animal experiments. It should prove a useful addition to the shelves of the pharmacological section in medical libraries. (J. & A. Churchill Ltd., price 25*s*.)

Inside the Living Cell, by J. A. V. Butler, D.SC., F.R.S., describes in non-technical language many of the recent advances in fundamental biology. As the title indicates, the greater part is devoted to cellular biochemistry and metabolism, a subject to which the author himself has made some outstanding contributions. Professor Butler, however, ranges widely and discusses subjects such as genes and mutations, viruses, vitamins and antivitamins, 'the brain and what it does'. Whilst written primarily for the intelligent layman, many a practitioner will enjoy dipping into its pages. (George Allen & Unwin, price 21*s*.)

Motherhood is the beautifully produced eighth edition of this well-known guide for expectant and nursing mothers. In addition to helpful advice on all aspects of the subject it includes a useful section on 'Precautions and First-Aid'. (Cow & Gate Ltd., Guildford, Surrey, price 1*s*.)

NOTES FROM THE CONTINENT

A European Newsletter

BELGIUM

Distomiasis.—In a communication to the Royal Academy of Medicine, Professor J. Roskam, of the University of Liège, has drawn attention to the occurrence of fluke infections in Belgium. In giving an account of a small outbreak of distomiasis in a village in the Ardennes, he drew attention to the absence of characteristic features in many of the cases—apart from the quite marked eosinophilia which was often present. On the basis of his experience he suggests that cases may often be missed. In drawing the attention of the public health authorities and doctors to the occurrence of distomiasis in Belgium, he particularly urges the discouragement of the eating of wild watercress as one of the most useful preventive measures.

The ballistocardiogram in coronary disease.—Attention is drawn by W. Cassiman and J. Enderle to the value of the ballistocardiogram in the diagnosis of coronary disease. In a series of 60 cases of myocardial infarction, and 30 cases of angina pectoris, they obtained an abnormal record in 52 of the former and in 29 of the latter. In a number of cases they found that the ballistocardiogram was more reliable than the electrocardiogram from the point of view of diagnosis as well as that of prognosis.

The action of busulphan.—Dr. Chevremont and his colleagues, of the University of Liège, have published a detailed account of the effect of busulphan on cellular histology and metabolism. In a study of the effect of busulphan on normal fibroblasts in tissue cultures they found marked chromosomatic changes including rupture and fragmentation and bridge formation. The extent of these changes was dependent upon the dose and the duration of exposure to the drug. Even with quite small doses, growth could be practically inhibited provided exposure to the drug was maintained for a sufficiently prolonged period. The action of busulphan is only upon the dividing cell. Even after exposure to busulphan for several hours the resting cell shows no changes—either nuclear or cytoplasmic. The metabolism of deoxyribonucleic acid (D.N.A.)

WHATEVER YOUR CHOICE

Austin £885.12.6

MORRIS £885.12.6

Ford £825.0.0

£912.10.0

FREE from purchase tax. In ready-for-the-road condition.

THE PITT

Moto-Caravan

gives you much more than any other vehicle today

The design of the 'PITT' Moto-Caravan, incorporating the ingenious and advanced ideas of Mr. Peter Pitt, today serves as an inspiration to the more recent manufacturers. The 'PITT' — first in the field — continues to lead.

The 'PITT' gives you more commonsense design for practical use—greater space and flexibility of arrangement — higher quality materials and obvious craftsmanship.

Drive and park your 'PITT' today and every day as you would your private car. No speed restrictions, 28-32 m.p.g. and you've also got an all-purpose mobile caravan when you want it. For touring, sport, weekends, etc. The 'PITT' is the most adaptable vehicle today.

The 'PITT' is the only design which will cater for single, double, twin and children's beds, dinette and day lounge at will.

For full details or demonstration contact your dealer or write for Leaflet "F 1" to

PITT MOTO-CARAVAN, 15-17, Southampton Mews, London, N.W.5. GULliver 6761-2

is also profoundly affected. Evidence is presented that the nuclear content of D.N.A. is increased as much as eightfold. There is no evidence of any increase in the number of chromosomes, and it is therefore suggested that the amount of D.N.A. per chromosome is increased.

Cardiomycoses.—In a review of mycotic infections of the heart, Professor R. Vanbreuseghem, of the Free University of Brussels and the Antwerp Institute of Tropical Medicine, notes that the most common forms are actinomycosis, blastomycosis, coccidioidomycosis, histoplasmosis, and moniliasis. The fungus can reach the heart either by the blood stream or by direct spread. The first of these is the common means of spread in the case of histoplasmosis and moniliasis, which explains why these two infections tend to produce endocardial lesions, whereas actinomycosis and coccidioidomycosis involve the heart by direct spread and therefore the lesions are predominantly found in the myocardium and pericardium. Predisposing factors to the development of cardiomycosis include diabetes mellitus, the use of antibiotics, and pre-existing endocardial lesions. This last factor is particularly important in the case of histoplasmosis and moniliasis, as the fungi in these two conditions seem to have particular difficulty in infecting an intact endocardium. As in the case of all mycotic infections, males are more commonly involved than females, and adults are more likely to be affected than children.

From the practical point of view the importance of mycotic infections of the heart is that they must always be borne in mind as the possible cause in cases of subacute bacterial endocarditis in which persistently negative blood cultures are obtained. In all such cases a careful search should be made for a fungus as the possible source of infection.

Tests for inebriety.—The measurement of alcohol in the expired air as a guide to the blood level of alcohol is an expensive waste of time, according to P. Moureau and his colleagues of the department of medico-legal medicine in the University of Liège. The conditions under which samples of air have usually to be collected for this purpose are such that the results are bound to be inaccurate. Apart from anything else, it is practically impossible to obtain adequate cooperation from the individual involved. It is much more satisfactory to proceed straight to the taking of a sample of blood for the estimation of the blood alcohol.

'*Notes from the Continent*' *are produced in collaboration with the Editors of* Bruxelles-Médical (*Belgium*), Le Concours Médical (*France*), Münchener Medizinische Wochenschrift (*Germany*), and Minerva Medica (*Italy*).

Your Guide, Sir?

To get the most out of your Continental holiday take a good guide. The finest guides are by

MICHELIN

GREEN GUIDES

Regional Guides to France :
CHATEAUX of the LOIRE
PARIS BRITTANY
FRENCH RIVIERA
12/6 each (*Postage 6d.*)
ITALY & SWITZERLAND
15/- each (*Postage 6d.*)

Send for latest list to the U.K. Distributors ; News Chronicle Book Department, Bouverie St., London, E.C.4

The Medical Service of the Royal Navy

VACANCIES FOR MEDICAL OFFICERS

Candidates are invited, for Short Service Commissions of 3 years, on termination of which a gratuity of £600 (tax free) is payable. Ample opportunity is granted for transfer to Permanent Commissions on completion of one year's total service. Officers so transferred are paid instead a grant of £1,500 (taxable).

All entrants are required to be British subjects whose Parents are British subjects, medically qualified, physically fit, and to pass an interview.

Full particulars from:
THE ADMIRALTY MEDICAL DEPARTMENT,
QUEEN ANNE'S MANSIONS,
ST. JAMES'S PARK,
LONDON, S.W.1

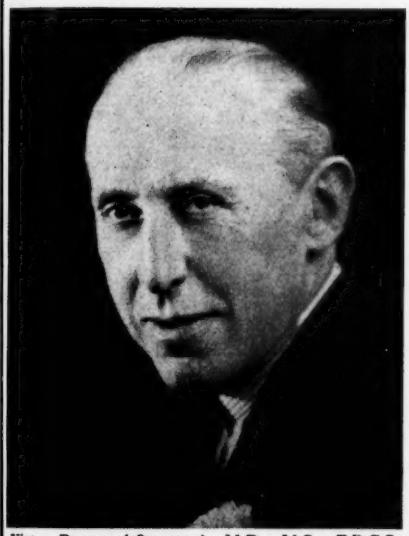
THE PRACTITIONER

Fifty Years Ago

'After a good dinner, one can forgive anybody, even one's own relations'.—Oscar Wilde, *A Woman of No Importance.*

JUNE, 1909

THE House Dinners of the Authors' Club, which was founded in 1891, are still reckoned among the more popular features of literary London. In an annotation entitled 'A Medical Night at the Authors' Club', 'Notes by the Way' fifty years ago tell us that this Club 'includes



Victor Bonney (1872-1953), M.D., M.S., F.R.C.S., F.R.C.O.G.

many medical members; so that, when Sir Almroth Wright was recently entertained there, at a dinner at which Dr. Tom Robinson took the chair, and expounded the principles of therapeutic inoculation, his audience was by no means exclusively composed of laymen, but also comprised many men of note in the medical world. Dr. R. W. Allen spoke, and so did the Chairman, and Dr. Brudenell Carter; while Lord Justice Fletcher Moulton helped to make technicalities comprehensible to the least scientific intelligence by a lucid and well sustained analogy between the invasion of the human body by pathogenic organisms, and an assumed invasion of Britain by a foreign foe . . . Both the enthusiasts and the sceptics were brilliantly represented . . . Dr. Brudenell Carter spoke with the gratitude of a patient, who had found the treatment a specific for catarrh, and felt that he need fear no foe of that sort in the future, provided that he kept a certain "sauce" where Mrs. Gamp used to keep her favourite restorative, and employed it, when "so dispoged", for the rectification of his opsonic index. We all, without exception, hope that his expectations will be justified'.

'Good mouth washes', The Editor states, 'are worth much, and cost little to prepare. Most of those in general use, however, are proprietary articles and cost a great deal to buy; and the layman, as a rule, has no means of knowing how any given mouth wash will affect the mucous membrane, or what is its bactericidal strength. He can only judge it by the price and the flavour . . . Three and sixpence for a bottle of which the value of the ingredients is fourpence is no uncommon discrepancy; and no-one can expect, say, a struggling clerk with a large family to give that family the run of a three-and-sixpenny dentifrice. He is far more likely . . . to confine them to precipitated chalk. Hence a great deal of the indigestion which abounds, to say nothing of graver maladies'.

The title of the final Editorial Note, 'The Dangers of X-Rays', sounds modern enough, but its contents are dated: 'A great deal of alarm appears to have been excited by the reports published of the injuries suffered by doctors through their use of the x-ray apparatus. If the doctor cannot protect himself, it is asked, how can he protect his patient? And is it not better to dispense with the facilities for diagnosis which the rays afford them to take the risk of a dermatitis not easily distinguishable from cancer? . . . The real risks . . . were taken by the pioneers, who did not know that they were taking risks, and consequently proceeded without adequate precautions. The nature and extent of the danger have now been determined . . . and effective precautions have been devised . . . Whether the subject is as yet sufficiently explored to justify the compulsory application of the rays to children suffering from ringworm, as the London County Council proposes, is another question'.

The opening article, 'The Bearings of Pathology on the Prevention, Diagnosis, and Surgical Cure of Carcinoma of the Cervix' is from the pen of Victor Bonney, M.D., M.S., M.R.C.P., F.R.C.S., Assistant Obstetric Physician to the Middlesex Hospital, and Senior

Surgeon to Out-Patients, Chelsea Hospital for Women: 'For the establishment of an operation fulfilling the demands of pathology, gynæcologists are principally indebted to Wertheim, whose operation, or some modification of it, appears to me to be destined to become the only one practised for the cure of carcinoma of the cervix'. Victor Bonney was appointed assistant gynæcological surgeon at the Middlesex in 1908 and, on the retirement of Sir Comyns Berkeley, was elected full gynæcological surgeon in 1930. A careful and infinitely gentle surgeon, he was 'the most skilful, experienced, and intrepid of all exponents throughout the world of the Wertheim operation' (Gordon-Taylor).

R. P. Rowlands, M.S., F.R.C.S., Surgeon-in-Charge of the Orthopædic Department, Guy's Hospital, discusses 'Some Points in the Treatment of Simple Fractures'; Frank E. Larkins, M.D., Assistant Education Medical Officer, Surrey, contributes a 31-page article on 'Cerebro-Spinal Fever'; J. H. Thursfield, M.D., F.R.C.P., Assistant Physician, Hospital for Sick Children, Great Ormond Street, reviews 'Diseases of Children'; and Arthur R. Littlejohn, M.R.C.S., L.R.C.P., M.R.C.V.S., deals with 'Meat as a Source of Infection in Tuberculosis'.

Among the books reviewed is 'Clinical Methods. A Guide to the Practical Study of Medicine' by Robert Hutchison and Harry Rainey: 'We are glad to see another edition of this book, which is already well known and appreciated . . . We are sure that the book will continue to be in demand as one of the best of the smaller works on the subject'. The reviewer, however, misses 'any mention of the very excellent way of estimating sugar, associated with the name of Bang a method which is rapidly replacing both Fehling's and Pavy's methods'. Bang's method, described by the Swedish biochemist, Ivar Bang, in 1907, is now quite obsolete, though it is still included in Dorland's Medical Dictionary. Benedict's reagent was introduced fifty years ago, in 1909. A number of eminent contributors are listed to Parts I and II of Volume IV of 'A System of Medicine by many Writers', edited by Sir Clifford Allbutt and Humphry Davy Rolleston: Morley Fletcher, Hale White, W. H. Hallburton, Bosanquet, Rose Bradford, Felix Semon.

'Practical Notes' mention a curious remedy for dysmenorrhœa: guaiacum resin, which, according to Dr. Herman, 'will, in some cases, prevent the pain from coming on, or lessen its severity when it does come. Ten grains should be administered three times a day, begun a week before menstruation is expected, and continued until the time, at which the pain usually occurs, is past'.

W. R. B.

NAPP

A reminder

"SOROSIL" Ointment

for the alleviation of all forms of Skin Itching

A germicidal, antiseptic, non-irritant ointment containing Chloral Hydrate, Camphor, Menthol, Ether, Iodine, Chloroform and Hyoscyamine. 'SOROSIL' gives rapid symptomatic relief in Pruritus, Prurigo, Eczema, Psoriasis, and in the dermal irritation associated with Chilblains, Urticaria, and Insect Bites.

Tube ½oz. Basic N.H.S. price 1s. 6d. + Tax. (Retail Price 2s. 0d. + Tax)

amples and literature available on request.

H. R. NAPP LIMITED · 3 & 4, CLEMENT'S INN · LONDON, W.C.2